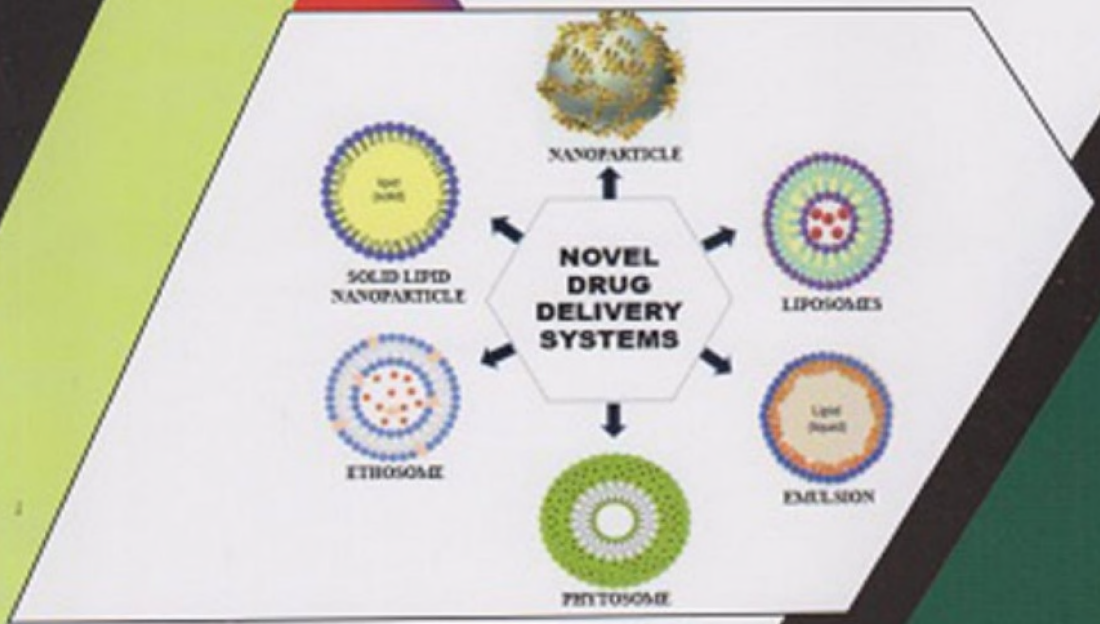
AS PER PCI REGULATIONS
FINAL YEAR B. PHARM.

SEMESTER
VII

NOVEL DRUG DELIVERY SYSTEMS

Dr. K. JESINDHA BEYATRICKS
Mrs. ASHWINI S. JOSHI



NIRALI PRAKASHAN
ADVANCEMENT OF KNOWLEDGE

A Text Book of

NOVEL DRUG DELIVERY SYSTEMS

As Per PCI Regulations

FINAL YEAR B. PHARM.

Semester - VII

Dr. K. Jesindha Beyatricks
M.Pharm., Ph.D.
Associate Professor,
Dept of Pharmaceutics,
Hillside College of Pharmacy and Research Centre,
Bangalore.

Mrs. Ashwini S. Joshi
M.Pharm.
Assistant Professor,
Dept of Pharmaceutics
S.E.T's College of Pharmacy,
S. R. Nagar, Dharwad, Karnataka.

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NIRALI PRAKASHAN
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N4379

Syllabus

BP 704T: NOVEL DRUG DELIVERY SYSTEMS (Theory)

Unit - I **10 Hours**

Controlled Drug Delivery Systems: Introduction, Terminology/Definitions and Rationale, Advantages, Disadvantages, Selection of Drug Candidates. Approaches to Design Controlled Release Formulations based on Diffusion, Dissolution and Ion Exchange Principles.

Physicochemical and Biological Properties of Drugs relevant to Controlled Release Formulations.

Polymers: Introduction, Classification, Properties, Advantages and Application of Polymers in Formulation of Controlled Release Drug Delivery Systems.

Unit - II **10 Hours**

Microencapsulation: Definition, Advantages and Disadvantages, Microspheres / Microcapsules, Microparticles, Methods of Microencapsulation, Applications.

Mucosal Drug Delivery system: Introduction, Principles of Bioadhesion/Mucoadhesion, Concepts, Advantages and Disadvantages, Transmucosal Permeability and Formulation Considerations of Buccal Delivery Systems.

Implantable Drug Delivery Systems: Introduction, Advantages and Disadvantages, Concept of Implants and Osmotic Pump.

Unit - III **10 Hours**

Transdermal Drug Delivery Systems: Introduction, Permeation through Skin, Factors Affecting Permeation, Permeation Enhancers, Basic Components of TDDS, Formulation Approaches.

Gastroretentive Drug Delivery Systems: Introduction, Advantages, Disadvantages, Approaches for GRDDS – Floating, High Density Systems, Inflatable and Gastroadhesive Systems and their Applications.

Nasopulmonary Drug Delivery System: Introduction to Nasal and Pulmonary Routes of Drug Delivery, Formulation of Inhalers (Dry Powder and Metered Dose), Nasal Sprays, Nebulizers.

Unit - IV **08 Hours**

Targeted Drug Delivery: Concepts and Approaches, Advantages and Disadvantages, Introduction to Liposomes, Niosomes, Nanoparticles, Monoclonal Antibodies and their Applications.

Unit - V **07 Hours**

Ocular Drug Delivery Systems: Introduction, Intra Ocular Barriers and Methods to Overcome – Preliminary Study, Ocular Formulations and Ocuserts.

Intrauterine Drug Delivery Systems: Introduction, Advantages and Disadvantages, Development of Intra Uterine Devices (IUDs) and Applications.

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Contents

POLYMERS

MUCOADHSIVE DRUG DELIVERY SYSTEM

BUCCAL DELIVERY SYSTEM

IMPLANTABLE DRUG DELIVERY SYSTEM

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Unit ... 1

CONTROLLED DRUG DELIVERY SYSTEMS

♦ LEARNING OBJECTIVES ♦

After completing this chapter, students will be able to:

- ❖ Explain basic concepts, advantages, disadvantages of controlled drug delivery system.
- ❖ Understand the factors influencing mechanism of Drug Delivery from CR formulation.
- ❖ Discuss the various approaches to design controlled release formulations based on diffusion, dissolution and ion exchange principles.
- ❖ Learn the physicochemical and biological approaches for CR formulation.
- ❖ Understand the criteria for selection of drugs and polymers.

1.1 INTRODUCTION

Oral administration of drugs has been the most common and preferred route for delivery of most therapeutic agents. It remains the preferred route of administration investigated in the discovery and development of new drug candidates and formulations. The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost-effective manufacturing methods and generally improved shelf-life of the product. For many drugs and therapeutic agents, conventional, multiple dosing of immediate release formulations provides satisfactory clinical performance with an appropriate balance of efficacy and safety.

The rationale for development of an extended release formulation of a drug is to enhance its therapeutic benefits, minimizing its side effects while improving the management of the diseased condition. Besides its clinical advantages, an innovative extended-release formulation provides an opportunity for a pharmaceutical company to manage its product life-cycle. The dearth of new chemical entities is forcing many pharmaceutical companies to reformulate an existing conventional formulation to an extended-release product as a strategy of life-cycle management and retaining market share. To imagine the ideal drug-delivery system, two prerequisites would be required:

1. It would be a single dose for the duration of treatment.
2. It should deliver the active entity directly to the site of action, thereby minimizing or eliminating side effects. Thus, the goal of sustained/controlled release dosage form is to maintain therapeutic blood or tissue levels of the drug over an extended period of time.

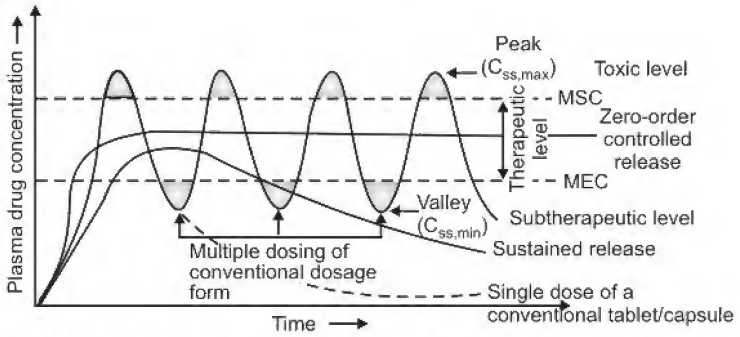


Fig. 1.1: Plasma Drug Concentration-Profiles for Conventional Tablet or Capsule Formulation, a Sustained Release Formulation and a Zero-Order Controlled Release Formulation

Figure 1.1 shows comparative blood drug level profiles obtained from administration of conventional, controlled as well as sustained release dosage forms. Thus, the conventional tablet provides only a single and transient burst of drug. A Pharmacological affect is seen as long as the amount of drug is within the therapeutic range. Pharmacological effect is altered when the peak concentration is above or below the therapeutic range. The main purposes of controlled release is to improve safety and minimize side effects of the drug by reducing fluctuation in drug level.

1.2 DIFFERENT TERMS USED UNDER NOVEL DRUG DELIVERY SYSTEMS

1. Delayed Release
2. Extended Release
3. Sustained Release
4. Controlled Release
5. Site Specific Targeting
6. Receptor Targeting
7. Fast Dissolve Drug Delivery System (Flash)

1.2.1 Delayed Release

A dosage form that releases a discrete fraction of drug at a time or times other than administration, although one portion may be released immediately after administration. Examples include; enteric coated tablets, where a timed release is achieved by barrier coating repeated action tablets or spansules.

1.2.2 Extended Release

When absorption of drug is greater than its elimination, the release is known as extended release. A dosage form should allow at least a twofold reduction in dosage

frequency as compared to that drug presented as an immediate release dosage form. These include; any dosage form that maintains therapeutic blood or tissue level of drug for prolong time.

1.2.3 Sustained Release

It includes the drug delivery systems that achieve and ensure slow release of drugs over an extended/prolonged period of time or at a constant release rate to attain and maintain therapeutically effective levels of drug concentration in the circulation. Here the absorption rate is equal to the elimination rate over an extended period of time.

1.2.4 Controlled Release

It includes any drug delivery system from which the drug is delivered at a predetermined rate over a prolong period of time.

1.2.5 Site Specific Targeting

It is a dosage form that releases drug at or near the intended physiologic site of action. Targeted release dosage forms may have either immediate or extended release characteristics. Targeted drug delivery is implicated by using carriers either meant for passive preprogrammed or active preprogrammed or self-programmed drug release approach. Thus, they are usually appended with suitable site directing molecules, which recognize their receptor or molecular determinants at the target.

1.2.6 Receptor Targeting

In such system, the target is a particular receptor within an organ or tissue.

1.2.7 Fast Dissolve Drug Delivery System (Flash)

It is type of solid dosage form that dissolves or disintegrate in the oral cavity without the help of water or chewing. Fast dissolution is achieved by forming loose network (Zydis, Eli Lilly), or by effervescent agent (Oraslav, Cima) or with mixture of disintegrating agent and swelling (Flash Tab, Prographarm).

1.3 RATIONALE OF CONTROLLED DRUG DELIVERY

The basic rationale of controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration.

The primary objectives of controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance. For conventional dosage forms only the dose and dosing interval can vary and for each drug, there exists a therapeutic window of plasma concentration below which therapeutic effect is insufficient and above which undesirable or toxic side effects are elicited. This is often defined as, "the ratio of median lethal dose (LD_{50}) to median effective dose (ED_{50})".

1.4 ADVANTAGES OF CONTROLLED DRUG DELIVERY

- Maintenance of drug levels within a desired range.
- Delivery of "difficult" drugs: slow release of water-soluble drugs, fast release of low solubility drugs.
- Less dosing and increased patient compliance.
- Eliminate overdosing or underdosing.
- Prevention of side effects.
- Reduction in health care cost.
- Improved efficiency in treatment.
- Reduction in adverse side effects and improvement in tolerability.

1.5 DISADVANTAGES OF CONTROLLED DRUG DELIVERY

- Dumping is a major disadvantage of CRDDS, which refers to the rapid release of a relatively large quantity of drug from a controlled release formulation. This phenomenon becomes hazardous with potent drugs.
- Poor in-vivo and in-vitro correlations.
- Difficult to optimize the accurate dose and dosing interval.
- Patient variability affects the release rate like GI emptying rate, residential time, fasting or non-fasting condition, etc.

1.6 FACTORS INFLUENCING THE DESIGN AND ACT OF CONTROLLED RELEASE PRODUCTS

1.6.1 Physiological Properties

(1) Aqueous solubility: Most of the active pharmaceutical moiety (API) are weakly acidic or basic in nature that affect the water solubility of API. Weak water-soluble drugs are difficult to design the controlled release formulations. High aqueous solubility drug show burst release followed by a rapid increment in plasma drug concentration. These types of drugs are a good candidate for CRDDS. The pH dependent solubility also creates a problem in formulating CRDDS. BCS class-III and IV drugs are not a suitable candidate for this type of formulations.

Determination of Solubility:

1. Semi-quantitative method.
2. Accurate-quantitative method.
3. pH change method.

Absorption of poorly soluble drugs is often dissolution rate-limited. Such drugs do not require any further control over their dissolution rate and thus may not seem to be good candidates for oral controlled release formulations. Controlled release formulations of such drugs may be aimed at making their dissolution more uniform rather than reducing it.

(2) Partition coefficient (P-value): P-value denotes the fraction of the drug into oil and aqueous phase that is a significant factor that affects the passive diffusion of the drug across the biological membrane. The drugs are having high or low P value not suitable for CR, it should be appropriate to dissolve in both phases.

The partition coefficient is defined as "the concentration ratio of unionized drug distributed between two phases at equilibrium".

- Given by the Noyes-Whitney's Equation:

$$P = \frac{[A]}{([A]\ \infty)}$$

- The logarithm (base 10) of the partition coefficient (log 10 P) is often used.
- For ionizable drugs, where the ionized species does not partition into the organic phase, the apparent partition coefficient, (D), can be calculated as:

  Acids: log 10 D = log 10 P – log 10 (1 + 10 (pH – pKa))

  Bases: log 10 D = log 10 P – log 10 (1 + 10 (pKa – pH))
- The octanol-water partition coefficient, has been widely used as a measurement for determining the relative lipophilicity of a drug. Drugs that are very lipid soluble or very water-soluble i.e., extremes in partition coefficient, will demonstrate:
  1. Either low flux into the tissues or
  2. Rapid flux followed by accumulation in tissues.
- Both cases are undesirable for controlled release system.

(3) Drug pKa: pKa is the factor that determine the ionization of drug at physiological pH in GIT. Generally, the high ionized drugs are poor candidates for CRDDS. The absorption of the unionized drug occurs rapidly as compared to ionized drugs from the biological membranes. The pKa range for an acidic drug that ionization depends on the pH is 3.0 to 7.5 and for a basic drug it lay between 7 and 11.

(4) Drug stability: Drugs that are stable in acid/base, enzymatic degradation, and other gastric fluids are good candidates for CRDDS. If drug is degraded in the stomach and small intestine, it is not suitable for controlled release formulations because it will decrease in bioavailability of concern drug.

(5) Molecular size and molecular weight: The molecular size and molecular weight are two important factors which affect the molecular diffusibility across a biological membrane. The molecular size less than 400D is easily diffused but greater than 400D create a problem in drug diffusion.

(i) In addition to diffusion through a variety of biological membranes, drugs in many CRDDS must diffuse through a rate controlling membrane or matrix.

(ii) The ability of drug to pass through membranes is called as diffusivity.

(iii) An important influence upon the value of diffusivity-D, in polymers is the molecular size of the diffusing species.

(iv) The value of D thus, is related to the size and shape of the cavities as well as size and shape of the drugs.

(v) Molecular size of the drug plays a major role when it comes to diffusion of the drug through a biological membrane.

(6) Protein binding: The drug-protein complex act as a reservoir in plasma for the drug. Drugs showing high plasma protein binding are not a good candidate for CRDDS because the protein binding increases the biological half-life. So, there is no need to sustain the drug release.

This complex leads to:

- Inhibition of therapeutic effect of such amount.
- Half-life is increased (compared to in vitro studies).
- Toxicity profiles elevated.

Thus, in most of the cases, protein binding is undesirable. Many drugs are highly protein bound (may be 95%), thus the need of formulating a modified drug or drug delivery system starts.

1.6.2 Biological Properties

(1) Absorption: Uniformity in rate and extent of absorption is an important factor in formulating the CRDDS. However, the rate limiting step is drug release from the dosage form. The absorption rate should rapid the release rate to prevent the dose dumping. The various factors like; aqueous solubility, log P, acid hydrolysis, which affect the absorption of drugs.

(2) Distribution: Distribution of drug from the conventional dosage form directly gets distributed throughout the body, and gets accumulated to some of the off-sites, which may lead to toxicity. Such instances can be prevented by CRDDS, which can be site-targeted and specific towards the diseases condition area and thus preventing accumulation in other sites.

It also enables the complete drug to be reached to the required site, unlike the conventional forms.

(3) Elimination: There are so many drugs available, which accumulates in the organs like; liver, pancreas, etc. and becomes fatal sometimes. Removal of such unwanted accumulated portion is quite hectic for the system due to slow elimination rate. In such cases, CRRDS again plays a major role as the accumulation in off-sites are comparatively negligible, and also the released drug easily expresses the action and then gets eliminated safely.

(4) Biological half-life ($t_{1/2}$): In general, the drug having short half-life requires frequent dosing and suitable candidate for controlled release system. A drug with long half-life requires dosing after a long-time interval. Ideally, the drugs having $t_{1/2}$ 2-3 hours, are a suitable candidate for CRDDS. Drugs having $t_{1/2}$ more than 7-8 hours are not used for controlled release system.

(5) Dose size: The CRDDS are formulated to eliminate the repetitive dosing, so it must contain the large dose than conventional dosage form. But the dose used in conventional dosage form give an indication of the dose to be used in CRDDS. The volume of sustained dose should be as large as it comes under acceptance criteria.

- Size of the drug plays a major role in determining the size of the final finished product.
- In case, the dose is already high, then formulating the same into controlled release will further increase the overall dosage size and thereby reduce patient compliance.
- For drugs with an elimination half-life of less than 2 hours, as well as those administered in large doses, a controlled release dosage form may need to carry a prohibitively large quantity of drug.

(6) Therapeutic window: The drugs with narrow therapeutic index are not suitable for CRDDS. If the delivery system failed to control release, it would cause dose dumping and ultimate toxicity.

(7) Absorption window: The drugs which show absorption from the specific segment in GIT, are a poor candidate for CRDDS. Drugs which are absorbed throughout the GIT are good candidates for controlled release.

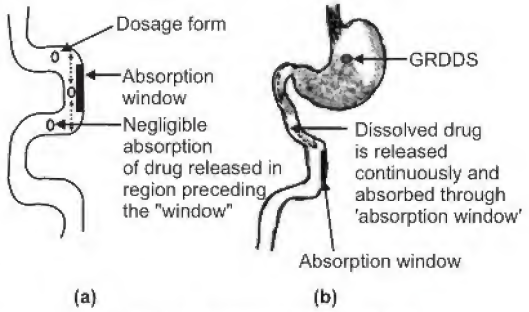


Fig. 1.2: Absorption Window

(8) Patient physiology: The physiological condition of the patient like gastric emptying rate, residential time, and GI diseases influence the release of the drug from the dosage form directly or indirectly.

Pharmacokinetic parameters considered during the drug selection are listed as follow:

Table 1.1: Pharmacokinetic Parameters for Drug Selection

Parameter	Comment
Biological or elimination half-life.	Should be between 2 to 6 hours.
Elimination rate constant (KE).	Required for design.
Total clearance (CLT).	Dose independent.
Intrinsic absorption rate.	Should be greater than the release rate.
Apparent volume of distribution (V_d).	V_d effect the required amount of the drug.
Absolute bioavailability.	Should be 75% or more.
Steady state concentration (C_{ss}).	Lower C_{ss} and smaller V_d.
Toxic concentration.	The therapeutic window should be broader.

1.7 FORMULATION ASPECTS INFLUENCING THE DESIGN OF ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

1.7.1 Drug Properties

Drug solubility and dose are the most important factors to be considered in the design of ER matrices. In general, extended-release formulation of extreme drug solubility's coupled with a high dose is challenging. Drugs with very low solubility (e.g. <0.01 mg/ml) may dissolve slowly and have slow diffusion through the gel layer of a hydrophilic matrix. Therefore, the main mechanism of release would be through erosion of the surface of the hydrated matrix. In these cases, the control over matrix erosion to achieve consistent extended release throughout the GI tract is critical. For drugs with very high-water solubility, the drug dissolves within the gel layer (even with small amount of free water) and diffuses out into the media. Therefore, it is important to control the factors that affect drug diffusivity (e.g. pH, gel strength and availability of free water) within the gel layer and parameters that ensure integrity of the gel layer after the drug has been dissolved and released from the gel layer. For poorly soluble drugs, particle size of the drug has a major influence on its release profile. A decrease in particle size of the drug causes increase in solubility and hence faster drug release rate.

1.7.2 Polymer Considerations

Depending on dosage size and desired release rate, the typical use level can vary from 20 to 50% (w/w). For drugs with high water solubility, there is a threshold level of polymer for achieving controlled release, and further increase in polymer level may not decrease the drug release rate. However, for obtaining a robust formulation with consistent performance and insensitivity to minor variations in raw materials or manufacturing processes, a usage level of 30% (w/w) has been recommended.

Particle size of the polymer is also an important factor. The finer the particle size, the faster the rate of hydration of the polymer and hence better the control of drug release. Coarser polymer particles used in a direct compression formulation have been reported to result in faster drug release than finer particles. The coarser the particle size, the slower the hydration rate and gel layer formation.

1.7.3 Presence of Other Excipients

Fillers:

Soluble fillers (e.g. lactose), insoluble fillers (e.g. microcrystalline cellulose, dicalcium phosphate) and/or partially soluble (e.g. partially pregelatinized starch). Fillers are generally used in hydrophilic matrices to enhance pharmaco-technical properties of tablets (improve compressibility, flow and mechanical strength) or to modify the drug release profile. The inclusion of fillers affects the dissolution performance of a matrix by a "dilution effect" on the polymer. The magnitude of the effect on the performance of matrices is dependent on the drug, the polymer level and the level of excipient itself. The presence of water-soluble

fillers in high concentrations in the matrix leads to faster and greater water uptake by the matrix, resulting in weaker gel strength, higher erosion of the gel layer and therefore faster drug release. Insoluble but weakly swellable fillers such as; microcrystalline cellulose remains within the gel structure and generally result in decreased release rate. The presence of partially pregelatinized starch such as; Starch 1500® in HPMC matrices has been reported to decrease the drug release rate. For a highly soluble or sparingly soluble drug, the rank order of release rate was as follows:

Lactose > Microcrystalline cellulose > Partially pregelatinized starch.

1.7.4 Release Modifiers and Stabilizers

Drugs with pH-dependent aqueous solubility (weak acids or bases) are formulated in HPMC matrices, they may exhibit pH-dependent drug release. Formulating CR matrices of such drugs may lead to lower drug release due to exposure of the dosage form to increasing pH media of the GI tract (from pH 1.2 to 7). Formulating pH-independent CR matrices for such drugs would not only ensure adequate release throughout the physiological pH, but also lower intra- and inter-patient variability. Development of such pH-independent matrices for weakly basic drugs has been shown with the incorporation of acidic excipients (weak acids or salts of strong acids) that lower the micro-environmental pH within the gel layer and thus maintain high local solubility of the drug independent of the external release media.

1.7.5 Effect of Salts and Electrolytes

In general, as the concentration of ions in a polymer solution increases, polymer hydration or solubility decreases. The amount of water available to hydrate the polymer is reduced because more water molecules are required to keep the ions in solution. Moreover, the types of ions in solution affect the polymer hydration to varying degrees. The susceptibility of cellulose ethers to ionic effects follows the lyo-tropic series of the ions (chloride < tartrate < phosphates and potassium < sodium). Changes in the hydration state of a polymer in solution are manifested primarily by changes in solution viscosity and turbidity or cloud point. At low ionic strengths, the polymer hydration is unaffected, but higher ionic strengths may lead to a loss of gel integrity of the matrix. The extent of this influence depends on the polymer type and lyotropic series of the ions. The effect of electrolytes or salts is important only in cases where high concentrations of salts or electrolytes are present as tablet components or as constituents of dissolution media. *In vivo* conditions, however, have fairly low ionic strength (ionic strength of gastrointestinal fluids, (0.01-0.15)) to affect the polymer hydration and have significant impact on release rate.

1.7.6 Characteristics of Dosage Form

Variation in tablet shape and size may cause changes in surface area available for drug release and hence influences drug release profiles from HPMC matrices. A constant surface area to volume ratio (S/V) of different size and shape tablets for a HPMC formulation would lead to similar drug release profiles. The size of the tablet may also dictate the polymer level requirement. Smaller tablets have been reported to require higher polymer content

because of their higher surface area to volume ratio and thus shorter diffusion pathways. One technology proposed for modifying the matrix surface area to volume ratio was by physical restriction of the swelling of hydrophilic matrix by partially coating the matrix with insoluble polymers or multi-layered tablets (Geomatrix® technology).

1.7.7 Presence of Coating

Application of film coatings to tablet formulations is a common practice in the pharmaceutical industry. Tablets are coated for a variety of reasons such as improving the stability of the formulation, taste masking, enhancing the aesthetic appearance, identification and branding, improving the packaging process or modifying drug release profile. Coating of hydrophilic matrices with water-soluble polymers such as; Opadry® or low-viscosity HPMC generally does not alter drug release profiles. Coating with water-insoluble polymers such as ethyl cellulose with or without permeability modifiers (e.g., low viscosity grades of HPMC or Opadry) may be used for modulating the drug release profile from HPMC matrices.

1.8 CLASSIFICATION OF ORAL CONTROLLED DRUG DELIVERY SYSTEM

1. Dissolution controlled systems
2. Diffusional systems
   (a) Reservoir devices (b) Matrix devices
3. Bio erodible and combination of diffusion and dissolution systems
4. Osmatically controlled systems
5. Ion-exchange systems
6. pH-independent formulations
7. Altered density formulations
   (a) High density approach (b) Low density approach

The majority of oral controlled release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastro-intestinal tract.

1.8.1 Dissolution-Controlled Systems

Controlled release preparations of drugs could be made by decreasing their rate of dissolution. The approaches to achieve this include preparation of appropriate salts or derivatives, coating the drug with a slowly dissolving material or incorporating it into a tablet with a slowly dissolving carrier.

Dissolution controlled systems can be made in several different ways: By alternating layers of drug with rate controlling coats, a pulsed delivery can be achieved. If the outer layer is a quickly releasing bolus of drug, initial levels of drug in the body can be quickly established with pulsed intervals following. An alternative method is to administer the drug as a group of beads that have coatings of different thicknesses. Since the beads have different coating thicknesses, their release will occur in a progressive manner. Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at later

times will be achieved from those with thicker coatings. This is the principle of the spansule technology or microencapsulation.

The dissolution process at a steady state is described by Noyes Whitney equation:

$$\frac{dC}{dt} = \frac{D \cdot A\,(C_S - C)}{h}$$

where, dC/dt = Dissolution rate

D = Diffusion coefficient of drug through pores

h = Thickness of the diffusion layer

A = Surface area of the exposed solid

C_s = Saturated solubility of the drug

C = Concentration of drug in the bulk solution

Based on the technical sophistication, it is classified as:

1. Matrix type
2. Encapsulation type

1.8.1.1 Matrix Type

Matrix dissolution devices are prepared by compressing the drug with slowly dissolving carrier into tablet.

Controlled dissolution by:

1. Altering porosity of tablet
2. Decreasing its wettability
3. Dissolving at slower rate

The drug release is determined by dissolution of the polymer.

Examples: Dimetane extencaps, Dimetapp extentabs.

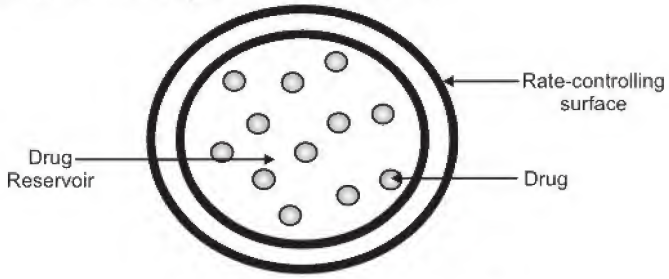


Fig. 1.3: Matrix Type Dissolution

1.8.1.2 Encapsulation Type

The drug particles are coated or encapsulated by microencapsulation technique. The pellets are filled in hard gelatin capsule, popularly called as 'spansules'. Once the coating material dissolves, the entire drug inside the microcapsule is immediately available for dissolution and absorption.

Here the drug release is determined by dissolution rate and thickness of polymer membrane which may range from 1 to 200 μ.

Dissolution rate of coat depends upon stability and thickness of coating.

Examples:

1. Ornade spansules.
2. Chlortrimeton repetabs.

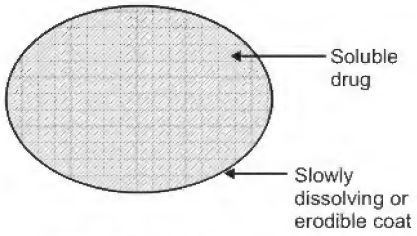


Fig. 1.4: Encapsulation Type

1.8.2 Diffusional Systems

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier. Usually, this barrier is an insoluble polymer. In general, two types of diffusional systems are recognized. They are reservoir device and matrix devices.

The release drug from a reservoir device follows Fick's first law of diffusion.

$$J = -D\frac{dc}{dx}$$

Where, J = Flux, amount/area-time

D = Diffusion coefficient of drug in the polymer, area/time

$\frac{dc}{dx}$ = Change in concentration with respect to polymer distance

1.8.2.1 Reservoir Devices

Reservoir devices are characterized by a core of drug, the reservoir, surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug from the system.

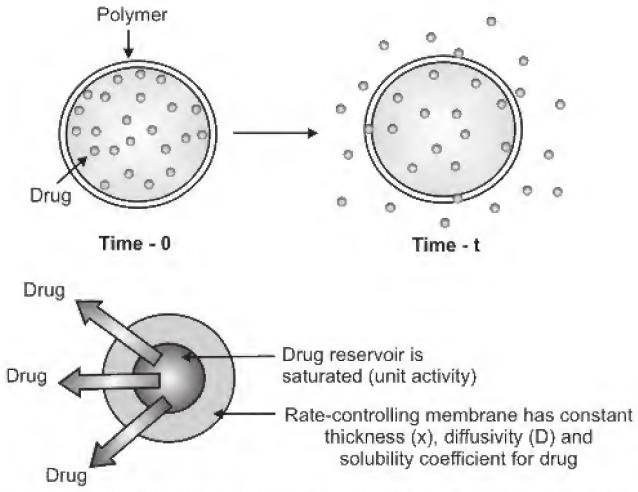


Fig. 1.5: Schematic Representation of Reservoir Diffusion Controlled Drug Delivery Device

The advantages of reservoir diffusional systems are, zero-order delivery are possible and release rate will vary with polymer type. The disadvantages of reservoir diffusional systems are, system must be physically plant site, difficult to deliver high-molecular weight compounds, rupture can result in dangerous dose dumping.

1.8.2.2 Matrix Devices

A matrix device consists of drug dispersed homogeneously throughout a polymer matrix. In this model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving towards the interior. Obviously, for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

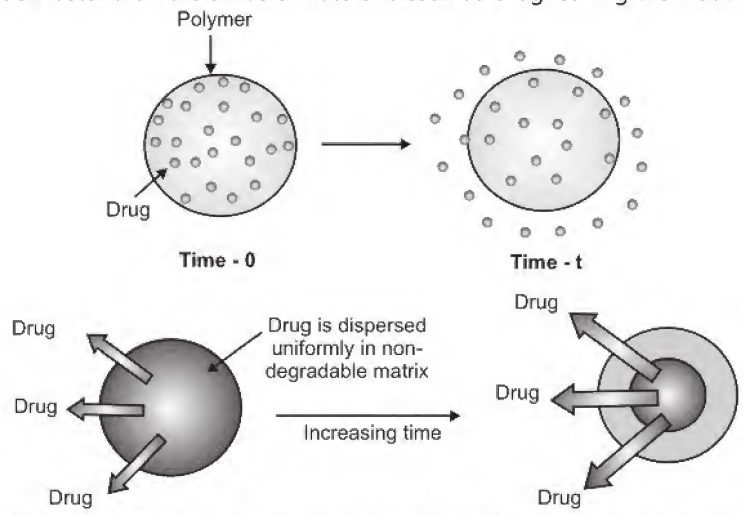


Fig. 1.6: Schematic Representation of Monolithic (Matrix) Diffusion Controlled Drug Delivery Device

1.8.3 Bio Erodible and Combination of Diffusion and Dissolution Systems

These systems can combine diffusion and dissolution of both the matrix material and the drug. Drug not only can diffuse out of the dosage form, as with some previously described matrix systems but the matrix itself undergoes a dissolution process. The complexity of the system varies from the fact that, as the polymer dissolves the diffusional path length for the drug may change. This usually results in a moving boundary diffusion system. Zero-order release can occur only if surface erosion occurs and surface area does not change with time. The inherent advantage of such a system is that, the bio erodible property of the matrix does not result in a ghost matrix and removal from implant sites is not necessary. The disadvantages of this system include, difficulty to control kinetics owing to multiple processes of release, potential toxicity of degraded polymer must be considered.

Another method of bio erodible system is to attach the drug directly to the polymer by a chemical bond. Generally, the drug is released from the polymer by hydrolysis or enzymatic reaction. A third type, which in this case utilizes a combination of diffusion and dissolution, is that of a swelling-controlled matrix.

Here the drug is dissolved in the polymer, but instead of an insoluble or eroding polymer, as in previous systems, swelling of the polymer occurs. This allows entrance of water, which causes dissolution of the drug and diffusion out of the swollen matrix. In these systems, the release rate is highly dependent on the polymer swelling rate, drug solubility and the amount of soluble fraction in the matrix. This system usually minimizes burst effects, since polymer swelling must occur before drug release.

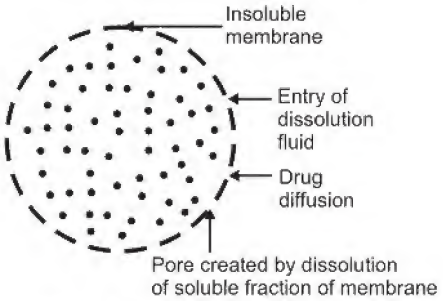


Fig. 1.7: Dissolution and Diffusion Controlled Release System

1.8.4 Osmotically Controlled Systems

In these systems, osmotic pressure provides the driving force to generate controlled release of drug. Consider a semi-permeable membrane that is permeable to water, but not to drug. A tablet containing a core of drug surrounded by such a membrane and when this device is exposed to water or any other body fluid, water will flow into the tablet owing to the osmotic pressure difference.

These systems generally appear in two different forms. The first one contains the drug as a solid core together with electrolyte, which is dissolved by the incoming water. The electrolyte provides the high osmotic pressure difference. The second system contains the drug in solution in an impermeable membrane within the device. The electrolyte surrounds the bag. Both systems have single or multiple holes bored through the membrane to allow drug release. In the first example, high osmotic pressure can be relieved only by pumping solution, containing drug, out of the hole. Similarly in the second example, the high osmotic pressure causes compression of the inner membrane and drug is pumped out through the hole.

The advantages of osmotically controlled devices are, zero-order release is obtainable. Reformulation is not required for different drugs and release of drug independent of the environment of the system. The disadvantages of these systems include, systems can be much more expensive than conventional counterparts and quality control is more extensive than conventional tablets.

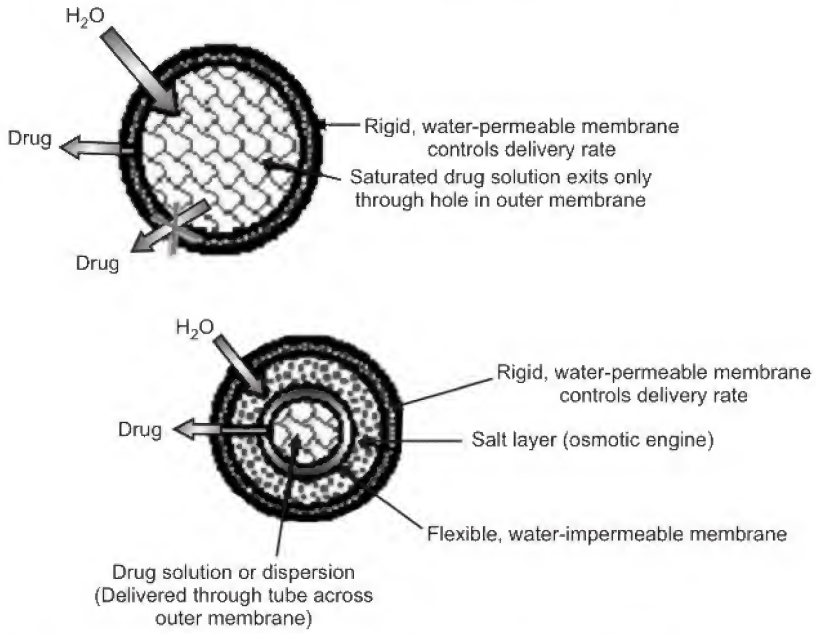


Fig. 1.8: Osmotically Controlled Release System

1.8.5 Ion-Exchange Systems

Ion-exchange systems generally use resins composed of water-insoluble, cross-linked polymers. These polymers contain salt-forming functional groups in repeating positions on the polymer chain. The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion-exchange groups.

$$Resin^+ - Drug^- + X^- \longrightarrow resin^+ - X^- + Drug^-$$

Conversely,

$$Resin^- - Drug^+ + Y^+ \longrightarrow Resin^- - Y^+ + Drug^+$$

Where, X^- and Y^+ are ions in the GI tract. The free drug then diffuses out of the resin. The drug-resin complex is prepared by mixing the resin with drug solution either by repeated exposure of the resin to the drug in a chromatography column or by prolonged contact in solution.

The date of drug diffusing out of the resin is controlled by the area of diffusion, diffusional path length and rigidity of the resin, which is a function of the amount of cross-linking agent used to prepare the resin.

This system is advantageous for drugs that are highly susceptible to degradation by enzymatic processes, since it offers a protective mechanism by temporarily altering the substrate. This approach to controlled release, however, has the limitation that the release rate is proportional to the concentration of the ions present in the area of administration.

Although the ionic concentration of the GI tract remains rather constant with limits, the release rate of the drug can be affected by variability in diet, water intake and individual intestinal content.

An improvement in this system is to coat the ion-exchange resin with a hydrophobic rate-limiting polymer, such as ethyl cellulose or waxes. These systems rely on the polymer coat to govern the rate of drug availability.

POLYMERS

1.9 INTRODUCTION OF POLYMERS

Polymers are compounds with high molecular masses formed by monomers. In Greek, the word poly means 'many' and meros means 'units or parts'. Polymers play a major role in the development of drug delivery technology by release of two types of drugs like; hydrophilic and hydrophobic in a synchronized manner and constant release of formulations over extended periods. There are numerous advantages of polymers acting as an inert carrier to which a drug can be conjugated, for example the polymer improves the pharmacokinetic and pharmacodynamic properties of biopharmaceuticals through various ways like; plasma half-life, decreases the immunogenicity, build ups the stability of biopharmaceuticals, improves the solubility of low molecular weight drugs, and has a potential of targeted drug delivery. However, they have their own limitations, such as; the natural polymers are most abundant and biodegradable but are difficult to reproduce and purify. Synthetic polymers have high immunogenicity, which prevent their long term usage. Non-biodegradable polymers are needed to be sugary after they release the drug at the targeted site. The general characteristic features that makes the polymer a potential candidate for drug delivery include; safety, efficacy, hydrophilicity, absence immunogenicity biological inactivity, sufficient pharmacokinetics and presence of functional groups for covalent conjugation of drugs, targeting moieties or formation of copolymer.

1.9.1 Characteristics of Ideal Polymer

1. Low density.
2. Low coefficient of friction.
3. Good corrosion resistance.
4. Good mould ability.
5. Excellent surface finish can be obtained.
6. Can be produced with close dimensional tolerances.
7. Economical.
8. Poor tensile strength.
9. Low mechanical properties.
10. Poor temperature resistance.
11. Can be produced transparent or in different colours.

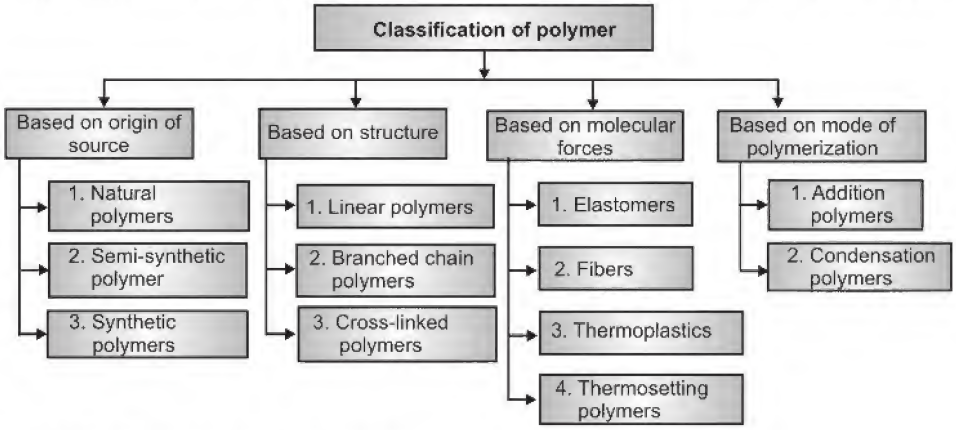
1.9.2 Advantages of Ideal Polymer

1. Polymers used in colloidal drug carrier systems, consisting of small particles, show great advantage in drug delivery systems because of optimized drug loading and releasing property.
2. A polymer (natural or synthetic) is aggregated with a drug in controlled drug delivery and hence it gives an effective and controlled dose of drug, avoiding overdose.
3. The degradable polymers are ruptured into biologically suitable molecules that are assimilated and discarded from the body through normal route.
4. Reservoir based polymers is advantageous in various ways like it increase the solubility of incompetently soluble drugs and it lowers the antagonistic side effects of drugs.
5. Magneto-optical polymer coated and targeted nanoparticles are multimodal (optically and MRI detectable) while Quantum Dots are only optically detectable.
6. Some Quantum dots contain C_d which is known to be toxic to humans. Magneto/optical nanoparticles whether polymer coated or targeted are composed of iron oxides/polymers which are known to be safe, therefore have great future.
7. Dextran is the common polymer used for coating of iron oxide (plasma expander and affinity for iron) and are used for treatment of iron anaemias since 1960 and is still in operation.
8. In controlled release, some of the polymers like; polyurethanes for elasticity, polysiloxanes for insulating ability are used for their intended non-biological physical properties.
9. Current polymers like; Poly 2-hydroxy ethyl methacrylate, Polyvinyl alcohol, Polyethylene glycol are used because of their inert characteristics and also, they are free of leachable impurities.
10. In biodegradable polymers, the system is biocompatible and it will not show dose leaving behind at any time, and the polymer will keep its properties until after exhaustion of the drug.
11. In hydrogels like drug delivery systems, the properties of polymer materials like PEG, (the easy polymer used to design hydrogels), can be managed to enhance features like; size of the pore, which is used to manage rate of diffusion of the conveyer drugs. PEGylation was considered to minister many diseases like; hepatitis B and C, neutropaenia connected with cancer chemotherapy (PEG-GCSF) 28 and various types of cancers [PEG] glutaminase merged with a glutamine anti-metabolite 6-diazo-5-oxo-norleucine (DON].
12. Polymers span from their use as films or binders covering agents in tablets to flow managing agent in liquids or emulsions for improving drug security and to alter the delivering characteristics. Micelles due to its smaller size have a small circulation time in the body. Hence, it results in an advantage of entering in the tumor cells easily, because of the EPR effect.

13. Large importance of polymers in drug delivery has been noticed because they give a distinctive property which so far is not achieved by any of the materials.
14. Polymers are preferable in the fact that they habitually show a pharmacokinetic profile as contrast to small-scale molecule drug with lengthy circulation time and they also have the ability for tissue targeting.
15. Gold nanoparticles are easy to prepare, good capability of co-existence, and their capacity to attach with other biomolecules without changing their properties.
16. Biggest benefit of utilizing polymers in drug delivery is their control (manipulation) on their properties (e.g. linkers and molecular weight) to modify to the need of drug delivery systems.

1.9.3 Polymer Classification

The polymers are classified in to various types based on different categories. They are:



1.9.3.1 Classification Based on Source

1. **Natural polymers:** These are derived from natural sources and can be polysaccharides and protein in chemical nature. For example: Albumin, Cellulose, Starch, Rubber, Wool.
2. **Semi-synthetic polymers:** These types of polymers are derived from naturally occurring polymers by means of chemical modifications. For e.g. Vulcanized rubber, Gun cotton, Cellulose diacetate, HPMC, etc.

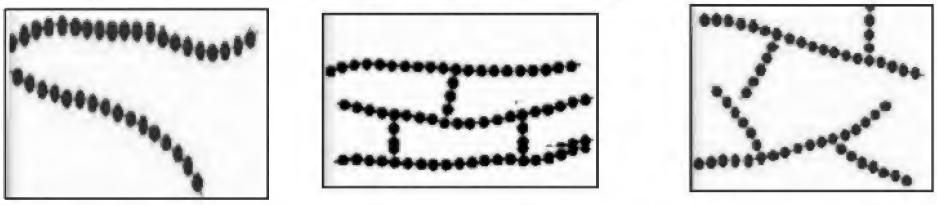
(i) Vulcanized rubber is used in making tyres as the process of vulcanization increases the mechanical strength of natural rubber.

(ii) Gun cotton which is a cellulose nitrate is used in making explosives. Cellulose on acetylation with acetic anhydride in the presence of sulfuric acid forms cellulose diacetate which is used in production of treads and materials like films, glasses, etc.

3. **Synthetic polymers:** Synthetic polymers are of artificial origin which consist of fibers. This is the polymer, which was prepared by Laboratory is known as Synthetic Polymer. For example: Buna-S, Buna-R, Nylon, Polythene, Polyester.

1.9.3.2 Classification Based on Structure

1. **Linear polymers:** The smallest repeating unit arranged in straight line path is known as Linear polymer. For example: PVC.
2. **Branched chain polymers:** Contain linear chains having some branches. For example: low density polymer, Polyethylene, HPLD polyethylene.
3. **Cross linked chain polymers:** In this type, all molecules are chemically bonded together, forming a three-dimensional network. The bonding is usually covalent but other types such as; ionic bond is also possible. Cross-linked polymers are produced from linear and branched polymers or directly from chemical precursor. For e.g. Natural rubber, polyacrylamide gels, epoxies, alkyd resins, etc.



Linear polymers | Cross-linked chain polymers | Branched chain polymers

Fig. 1.9: Classification Based on Structure

1.9.3.3 Classification Based on Polymerization

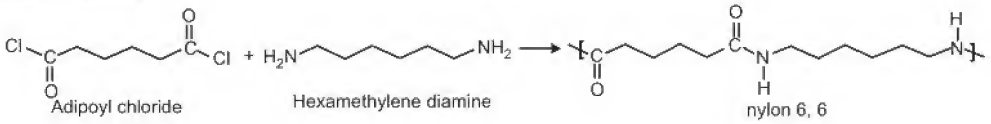
1. Additional polymers: Additional polymers are formed by the repeated addition of monomer molecules possessing double or triple bonds.

$$n(CH_2 = CH_2) - (CH_2 - CH_2)-$$

Ethylene polyethylene, one form of polymer is converted into another form of polymer by loss of atoms and ions from molecule.

2. Condensation polymers:

Condensation polymers formed by repeated condensation reaction between two different bi-functional or tri- functional monomeric units. For e.g. terylene (dacron), nylon 6, 6, One polymer can be converted into anther form of polymer without loss of atoms and ions from molecule.



Adipoyl chloride | Hexamethylene diamine | nylon 6, 6

1.9.3.4 Classification Based on Molecular Force

1. Nylon:

Nylon is used as general name for all synthetic fiber forming polyamides, having a protein like structure. These are the condensation polymers of diamine and dibasic acids. A number is usually suffixed with the Nylon which refers to the number of carbon atoms present in the diamine and the dibasic acids respectively.

For example: Nylon 6, 6. Nylon-6, 6 is obtained by the polymerization of adipic acid with hex methylene diamine.

2. Thermoplastic polymers:

These are linear or slightly branched long chain polymers, which can be softened on heating and reversibly hardened on cooling repeatedly. Their hardness is a temporary property and varies with temperature.

The polymer under heating can convert from one state to another state and after cooling, it can again convert to its original state.

For example: polyvinyl chloride.

1.9.4 General Mechanism of Drug Release from Polymer

Three primary mechanisms for drug release, namely:

1. Diffusion
2. Degradation
3. Water penetration (Swelling)

1.9.4.1 Drug Release from Polymer by Diffusion

Rate limiting step is diffusion of drug through inert water insoluble membrane barrier.

There are of two types:

1. Reservoir
2. Matrix

1. Reservoir Diffusion System:

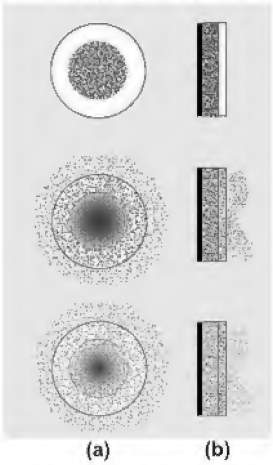


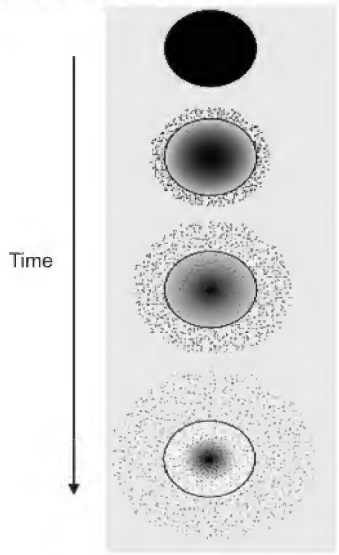
Fig. 1.10: Reservoir Diffusion System

In membrane-controlled reservoir devices, the drug is contained in a core, which is surrounded by a polymer membrane, and it is released by diffusion through this rate controlling membrane.

For example, Poly (N-vinyl pyrrolidone), Poly (ethylene-co-vinyl acetate).

Drug delivery from typical reservoir devices: (i) Implantable or oral systems, and (ii) Transdermal systems.

2. Matrix Diffusion System:



In these devices, the drug is released either by passing through the pores or between polymer chains, and these are the processes that control the release rate.

For example, polyethylene, polyvinyl acetate.

Fig. 1.11: Matrix Diffusion System

1.9.4.2 Degradation

Bio degradation is the chemical changes that alter the molecular weight or solubility of the polymers. Bio erosion may refer to as physical process that result in weight loss of a polymer device. The possibility for a polymer to degrade and to have its degradation by products assimilated or excreted by living system is designated as Bioresorbable.

The erosion of polymers basically takes place by two methods:

1. Chemical erosion
2. Physical erosion

1. Chemical Erosion:

Bio erosions through chemical mechanisms are explained below:

Mechanism-I:

It describes the degradation of water-soluble macromolecules that are cross-linked to form three-dimensional network.

Degradation in these systems can occur by:

- **Type (1A):** Degradation occur at crosslinks to form soluble backbone polymeric chains. It provides high molecular weight, water soluble fragments.
- **Type (1B):** Degradation occur to form water-soluble fragments. Such type provides low molecular weight, water soluble oligomers and monomers.

Mechanism-II:

Describes the dissolution of water insoluble macromolecules with side groups that are converted to water insoluble polymers as a result of ionization, protonation or hydrolysis of the groups.

Materials showing this type of erosion include;

- Cellulose acetate derivatives,
- Co-polymers of maleic anhydride.

Mechanism-III:

Describes the degradation of insoluble polymers with liable bonds. It forms low molecular weight, water soluble molecules.

Polymers undergoing this type of erosion include;

- Poly(lactic acids)
- Poly(glycolic acid) and their co-polymers, etc.

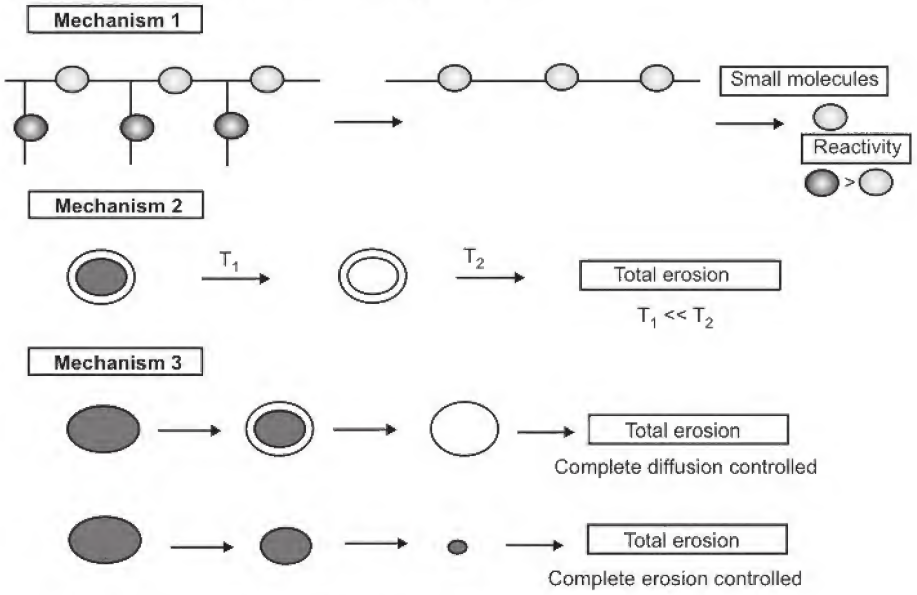


Fig. 1.12: Mechanism of Erosion of Polymers

2. Physical Erosion:

The physical erosion mechanisms can be characterized as heterogeneous or homogeneous.

- Most polymers undergo homogenous erosion that means the hydrolysis occur at even rate throughout the polymeric matrix.
- In homogenous erosion, there is loss of integrity of the matrix or polymer.
- In heterogeneous erosion, also called as surface erosion, the matrix degrades and the drug is released from the surface
- Highly crystalline polymers tend to undergo heterogeneous erosion.

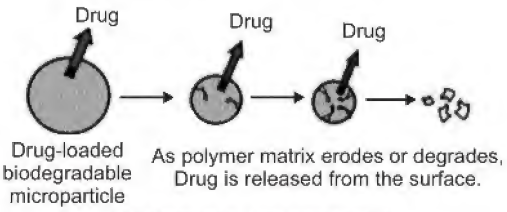


Fig. 1.13: Biodegradation

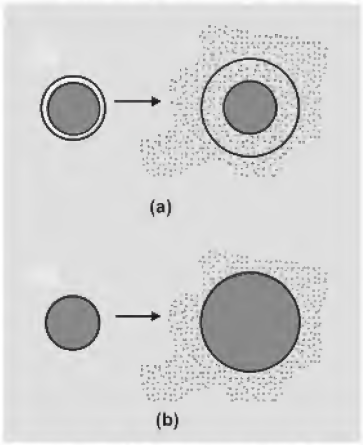
1.9.4.3 Water Penetration (Swelling)

These types of systems are initially dry and when placed in body, absorb water or other fluid and it swells. In swelling controlled release systems, an active agent is homogenously dispersed in a glassy polymer, because glassy polymers are essentially impermeable, the active agent is immobilized in the matrix and the diffusion through the solid polymer phase takes place.

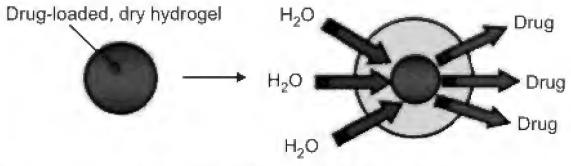
When a monolithic devices are placed in an aqueous environment, water begins to penetrate the matrix and swelling takes place. As a consequence of the swelling process, chain relaxation takes place and the incorporated active agent begins to diffuse from the swollen layer.

In linear amorphous polymers, dissolution follows the swelling process, but crosslinked polymers or those containing significant chain entanglements or partial crystallinity will remain insoluble but will be mechanically week.

Swelling increases aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into external environment. For example: (N-isopropyl-acrylamide), Ethylene-vinyl alcohol.



(i) Drug Delivery From (a) Reservoir, (b) Matrix Swelling-Controlled Release Systems



(ii) A Typical Oral Tablet/Pill

Fig. 1.14

1.9.5 Role of Polymers in Drug Delivery

(a) Immediate drug release dosage form tablets:

Polymers including; polyvinyl pyrrolidone and hydroxypropyl methyl cellulose (HPMC) are found to be a good binder which increases the formation of granules that improves the flow and compaction properties of tablet formulations prior to tableting.

(b) Capsules:

Many of the polymeric excipients used to "bulk out" capsules fills are the same as those used in intermediate release tablets. For hard and soft shell, gelatin is most often used. By recent advances, HPMC has been accepted as alternative material for hard and soft capsules.

(c) Modified drug release dosage forms:

To achieve gastro-retention, mucoadhesive and low density polymers have been evaluated their ability to extend gastric residence time by bonding to the mucus lining of the stomach and floating on top of the gastric contents respectively.

(d) Extended release dosage forms:

Extended and sustained release dosage forms prolong the time that, systemic drug levels are within the therapeutic range and thus reduce the number of doses the patient must take to maintain a therapeutic effect there by increasing compliance. The most commonly used water insoluble polymers for extended release applications are, the ammonium ethacrylate copolymers, cellulose derivatives; ethyl cellulose and cellulose acetate, and polyvinyl derivative; polyvinyl acetate.

(e) Gastro retentive dosage forms:

Gastro retentive dosage forms offer an alternative strategy for achieving extended release profile, in which the formulation will remain in the stomach for prolonged periods, releasing the drug *insitu*, which will then dissolve in the liquid contents and slowly pass into the small intestine.

1.9.6 Applications of Polymers in Formulation of Controlled Drug Delivery System

1.9.6.1 Osmotic Pressure-Controlled GI Delivery System

Semi-permeable membrane is made from biocompatible polymers.

E.g. cellulose acetate

Example of such type of system include, Acutrim tablet which contains Phenylpropanolamine as a drug.

In this device, an osmotic agent is contained within a rigid housing and is separated from an active agent compartment-b, a movable partition. One wall of the rigid housing is a semi-permeable membrane so that when the pump is exposed to an aqueous environment, water will be driven osmotically across the membrane, the increased volume within the osmotic compartment will force the active agent out of the device through the delivery orifice. Major application is for gastro intestinal drug deliveries because delivery rate is pH independent.

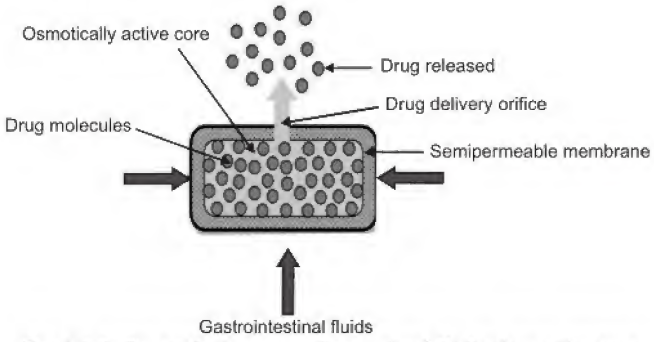


Fig. 1.15: Osmotic Pressure-Controlled GI Delivery System

1.9.6.2 Gel Diffusion Controlled GI Delivery System

Diffusion and Dissolution-Controlled Release System:

1. Drug is encased in a partially soluble membrane.
2. Pores are created due to dissolution parts of membrane.
3. It permits entry of aqueous medium into core and drug dissolution.
4. Diffusion of dissolved out of system.

Example: Ethyl cellulose and PVP mixture dissolves in water and create pores of insoluble ethyl cellulose membrane.

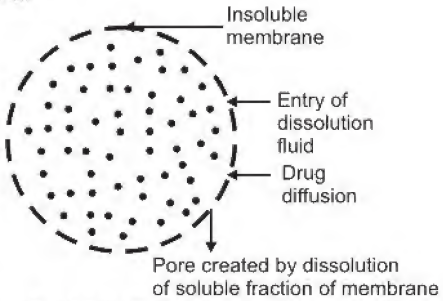


Fig. 1.16: Gel Diffusion-Controlled GI Delivery System

1.9.6.3 Mucoadhesive GI Delivery System

The new generation mucoadhesive polymers for buccal drug delivery with advantages such as; increase in the residence time of the polymer, penetration enhancement, site specific adhesion and enzymatic inhibition, site specific mucoadhesive polymers will undoubtedly be utilized for the buccal delivery of a wide variety of therapeutic compounds. The class of polymers has enormous potential for the delivery of therapeutic macromolecules.

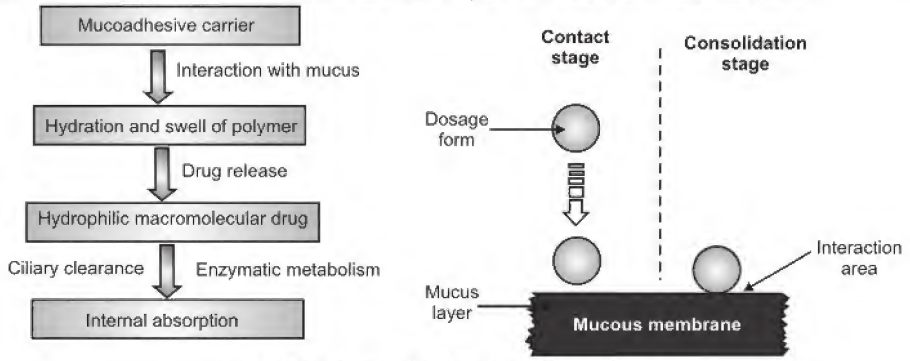


Fig. 1.17: Mucoadhesive GI Delivery System

1.9.6.4 Transdermal Drug Delivery System

TDDS is defined as, self-contained, self-discrete dosage forms, which when applied to the intact skin, delivers the drug at a controlled rate to the systemic circulation. In this, polymer matrix plays a major role. It releases the drug from the device to the skin.

Advantages of Transdermal Drug Delivery System:

- They permit easy removal and termination of drug action in situation of toxicity.
- Problems encountered with oral administration like; degradation, gastric irritation, etc. are avoided.

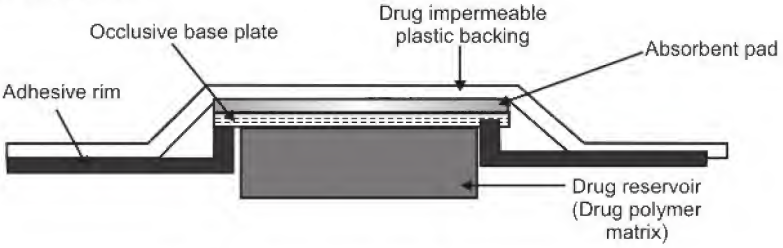


Fig. 1.18: Transdermal Drug Delivery System

1.9.6.5 Ocular Drug Delivery System

It allows prolonged contact of drug with corneal surface of eye. The example for ODDS is pilocarpine in the treatment of glaucoma. In this, muco-adhesive polymers are used as barriers to control the drug release. For e.g. Polyacrylic acid, Co polymers of acetate vinyl and ethyl.

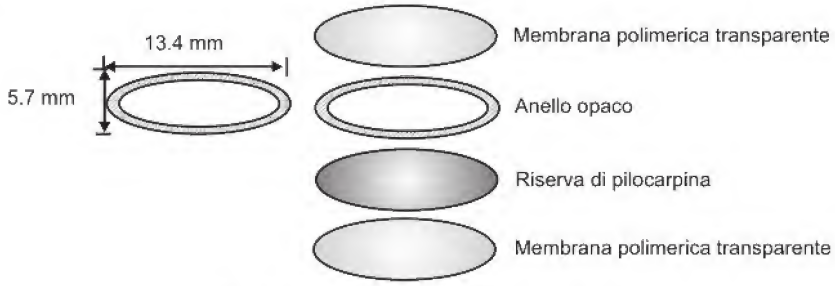


Fig. 1.19: Ocular Drug Delivery System

1.9.6.6 Other Applications

1. Drug Delivery and the Treatment of Diabetes:

Here the polymer will act as a barrier between blood stream and insulin.

E.g. Polyacrylamide or N,N-Dimethyl amino ethylmetha acrylate.

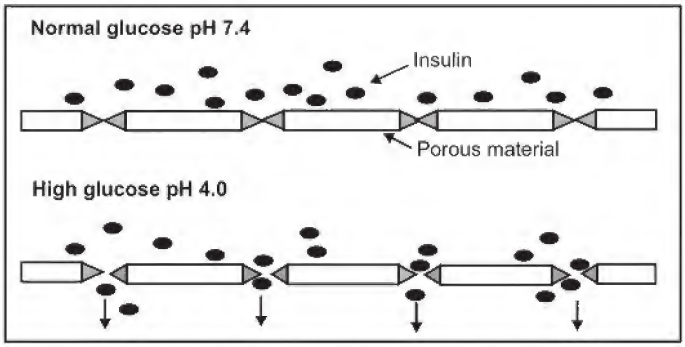


Fig. 1.20: Drug Delivery in the Treatment of Diabetes

2. Drug Delivery of Various Contraceptives and Hormones

It consists of drug saturated liquid medium encapsulated in polymeric layer which controls the concentration and release of drugs into the blood stream.

E.g. Medoxy progesterone acetate, Progestasert, Duromine, etc.

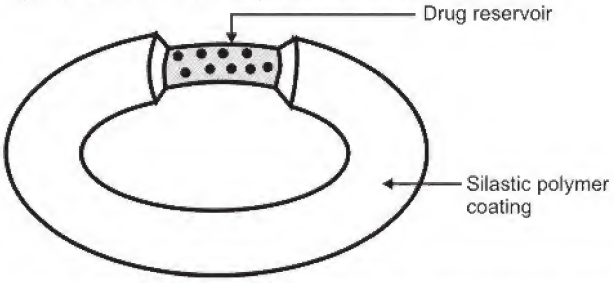


Fig. 1.21: Drug Delivery of Various Contraceptive and Hormones

QUESTIONS

1. Define Controlled release DDS. List out their advantages and disadvantages.
2. Describe the rationale behind the development of control release formulations.
3. Explain the principles behind the development of control release formulations.
4. List out and briefly explain the factors influencing the design and performance of controlled release products.
5. Explain the physicochemical properties of drugs to be considered when selecting them for formulation into CR dosage forms.
6. Explain why the biological properties should be considered when selecting drug candidates for CR drug delivery systems?

7. Define dissolution controlled DDS. Explain the principles and approaches used in their design.
8. Explain the mechanism of drug release from diffusion controlled DDS. List out their advantages and disadvantages.
9. Explain the principle of drug release from bioerodible DDS and the parameters that can be controlled.
10. Explain an ion exchange controlled drug delivery systems.
11. Define polymers. Briefly explain their role in the design of CR DDS.
12. Classify polymers with examples.
13. Elaborate on the applications of polymers in CR/SR DDS with suitable examples.

***

Unit ... 2

MICROENCAPSULATION

♦ LEARNING OBJECTIVES ♦

After completing this chapter, student will be able to:

- ❖ Explain the methods of microencapsulation and applications.
- ❖ Understand the principle and concept of mucoadhesion.
- ❖ Explain the transmucosal permeability and formulation considerations of buccal delivery systems.
- ❖ Understand the concept of implants and osmotic pump.

2.1 INTRODUCTION OF MICROENCAPSULATION

Microencapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules, of many useful properties. In general, it is used to incorporate food ingredients, enzymes, cells or other materials on a micro metric scale.

Microencapsulation may be defined as, "the process of surrounding or enveloping one substance within another substance on a very small scale, yielding capsules ranging from less than one micron to several hundred microns in size". It is mean of applying thin coating to small particle of solid or droplet of liquid and dispersion.

Microencapsulation is a process by which solids, liquids or even gases may be enclosed in microscopic particles by formation of thin coatings of wall material around the substances.

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000 μm. The range of Techniques for the preparation of microspheres offers a variety of opportunities to control aspects of drug administration and enhance the therapeutic efficacy of a given drug. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest. It also has advantage over liposomes as it is physico-chemically more stable. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumor.

There are two phases:

(a) Core material (b) Coating material

The product obtained by this process is called as micro particles, microcapsules, microsphere, coated granules, and pellets. Particles having diameter between 3-800 μm are known as microparticles or microcapsules or microspheres. Particles larger than 1000 μm are known as macroparticles.

2.2 ADVANTAGES OF MICROENCAPSULATION

1. Reliable means to deliver the drug to the target site and to maintain the desired concentration at the site of interest without untoward effects.
2. Solid biodegradable microspheres have the potential throughout the particle matrix for the controlled release of drug.
3. Microspheres received much attention for targeting of anticancer drugs to the tumor.
4. Reduces the dosing frequency and thereby improve the patient compliance.
5. They could be injected into the body due to the spherical shape and smaller size.
6. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
7. Microsphere morphology allows a controllable variability in degradation and drug release.

2.3 DISADVANTAGES OF MICROENCAPSULATION

1. It is an expensive process.
2. Requires skill.
3. Difficult to obtain continuous and uniform film.

2.4 REASONS FOR MICROENCAPSULATION

1. To protect reactive substances from the environment.
2. To convert liquid active components into a dry solid system.
3. To separate incompatible components for functional reasons
4. To protect the immediate environment of the microcapsules from the active components.
5. Isolation of core from its surroundings, as in isolating vitamins from the deteriorating effects of oxygen.
6. Retarding evaporation of a volatile core.
7. Improving the handling properties of a sticky material.
8. Isolating a reactive core from chemical attack.
9. For safe handling of the toxic materials.
10. To get targeted release of the drug.
11. To control release of the active components for delayed (timed) release or long-acting (sustained) release.

12. The problem may be as simple as masking the taste or odor of the core.
13. To Increase of bioavailability.
14. To produce a targeted drug delivery.
15. Protects the GIT from irritant effects of the drug.
16. Extension of duration of activity for an equal level of active agent.

2.5 FORMULATION CONSIDERATION

Generally Micro particles consist of two components:

(a) Core material:

The solid core can be mixture of active constituents, stabilizers, diluents, excipients and release-rate retardants or accelerators.

(b) Coat or wall or shell material:

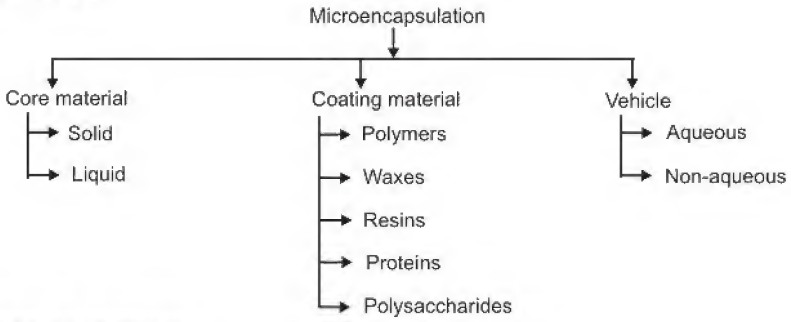
Compatible, non-reactive with core material. Provide desired coating properties like; strength, flexibility, impermeability, optical properties, non-hygroscopicity, tasteless and stable.

2.5.1 Core Material

The material to be coated. It may be liquid or solid or gas. Liquid core may be dissolved or dispersed material.

Composition of Core Material:

1. Drug or active constituent.
2. Additive like diluents.
3. Stabilizers.



2.5.2 Coating Material

Inert substance which coats on core with desired thickness.

Composition of Coating:

1. Inert polymer.
2. Plasticizer.
3. Colouring agent.
4. Resins, waxes and lipids.
5. Release rate enhancers or retardants.

(a) Role of Polymers:

Polymers are substances of high molecular weight made up by repeating monomer units. Polymer molecules may be linear or branched, and separate linear or branched chains may be joined by crosslinks.

Polymers are used widely in pharmaceutical systems as: adjuvants, coating materials and, a component of controlled and site-specific drug delivery systems.

(b) Coating Material Properties:

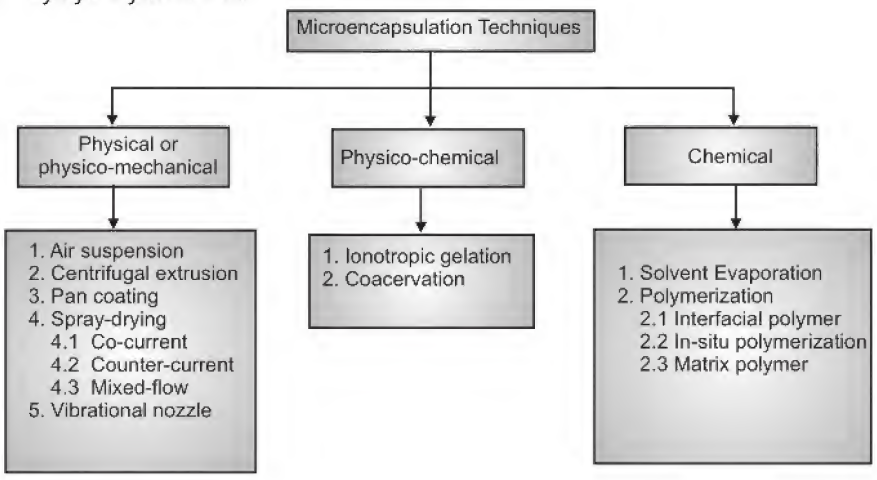
1. Stabilization of core material.
2. Inert toward active ingredients.
3. Controlled release under specific conditions.
4. Film-forming, pliable, tasteless, stable.
5. Non-hygroscopic, no high viscosity, economical.
6. Soluble in an aqueous media or solvent, or melting.
7. The coating can be flexible, brittle, hard, thin, etc.

2.6 RELEASE MECHANISMS

Even when the aim of a microencapsulation application is the isolation of the core from its surrounding, the wall must be ruptured at the time of use.

A variety of release mechanisms have been proposed for microcapsules:

1. By pressure or shear stress.
2. By melting the wall.
3. By dissolving it under particular conditions, as in the case of an enteric drug coating.
4. By solvent action.
5. By enzyme attack.
6. By chemical reaction.
7. By hydrolysis or slow.



2.6.1 Air Suspension Techniques (Fluidized Bed Coating)

Inventions of Professor Dale E. Wurster:

Basically, the wurster process consists of the dispersing of solid, particulate core materials in a supporting air stream and the spray-coating of the air suspended particles. Equipment ranging in capacities from one pound to 990 pounds.

Micron or submicron particles can be effectively encapsulated by air suspension techniques. Within the coating chamber, particles are suspended on an upward moving air stream.

The design of the chamber and its operating parameters effect a recalculating flow of the particles through the coating zone portion of the chamber, where a coating material, usually a polymer solution, is spray applied to the moving particles.

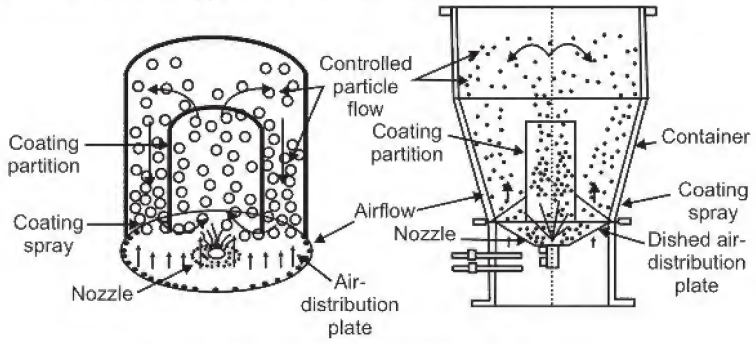


Fig. 2.1: Fluidized Bed Coating

2.6.1.1 The Wruster Process

1. This technology is characterized by the location of a spray nozzle at the bottom of a fluidized bed of solid particles.
2. The particles are suspended in the fluidizing air stream that is designed to induce a cyclic flow of the particles past the spray nozzle.
3. The nozzle sprays an atomized flow of coating solution, suspension, or other coating vehicle.
4. The technology can be used to encapsulate solid materials with diameters ranging from near 50 μm to several centimeters.
5. Wruster Process can be used to encapsulate vitamins, minerals, and functional food ingredients.

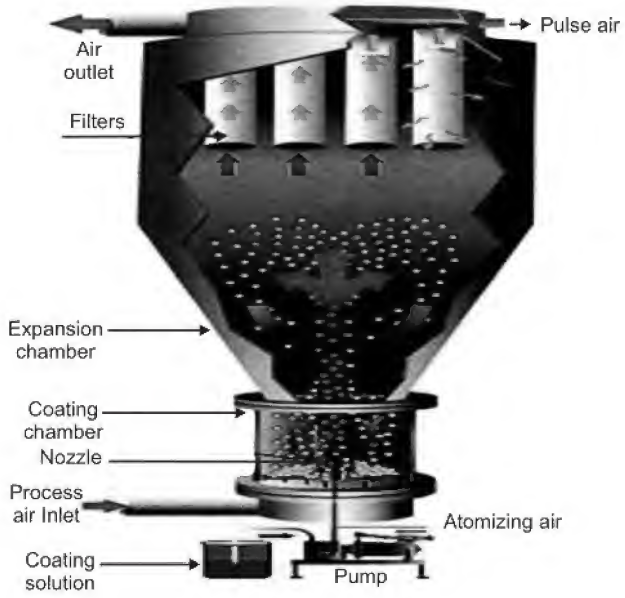


Fig 2.2: Wruster Process

6. It consists of dispersing the solid particulate core material in supporting air stream and being coated with coating material (usually polymeric solution).
7. In this, the fine core materials are suspended in a vertical current of air and sprayed with the coating material.
8. After evaporation of solvent, a layer of encapsulating material is deposited on core.
9. Gives improved control and flexibility as compared to pan coating.
10. During each pass through the coating zone, the core material receives an increment of coating material.
11. The cyclic process is repeated, perhaps several hundred times during processing, depending on the purpose of microencapsulation the coating thickness desired or whether the core material particles are thoroughly encapsulated.
12. The supporting air stream also serves to dry the product while it is being encapsulated.
13. Drying rates are directly related to the volume temperature of the supporting air stream.

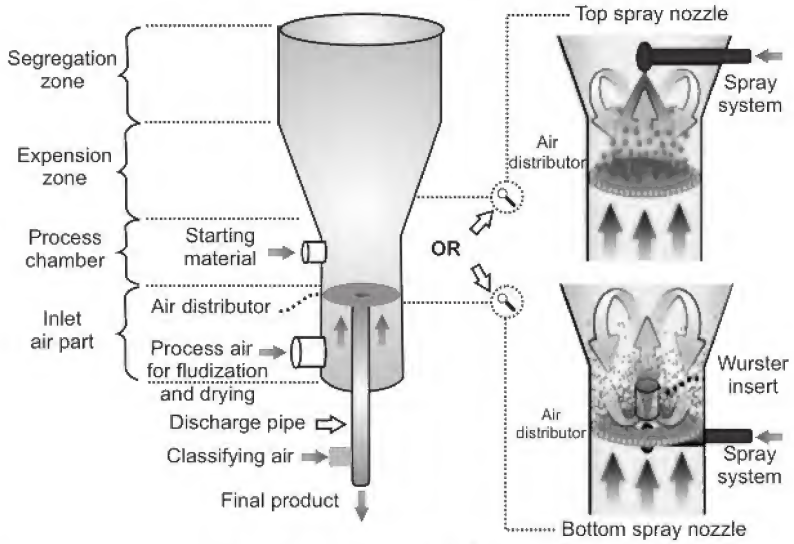


Fig. 2.3: Air Suspension Techniques

Disadvantage:

Agglomeration of the particles to some larger size is normally achieved.

Variables for Efficient, Effective Encapsulation by Air Suspension Techniques:

1. Density, surface area, melting point, solubility, friability, volatility, crystallinity and flow-ability of core the core material.
2. Coating material concentration (or melting point if not a solution).
3. Coating material application rate.
4. Volume of air required to support and fluidizes the core material.
5. Amount of coating material required.
6. Inlet and outlet operating temperatures.

2.6.2 Pan Coating

1. Oldest industrial procedures for forming small, coated particles or tablets.
2. The particles are tumbled in a pan or other device while the coating material is applied slowly.
3. Solid particles greater than 600 microns in size are generally considered essential for effective coating.
4. Medicaments are usually coated onto various spherical substrates such as; nonpareil sugar seeds, and then coated with protective layers of various polymers.
5. It is used for preparation of controlled- release beads.
6. Coating is applied as solution by automized spray to desired solid core material in coating pan.

7. Usually warm air is passed over the coated material as the coating are being applied in the coating pan.
8. Solid particles are mixed with a dry coating material.
9. The temperature is raised so that the coating material melts and encloses the core particles, and then is solidified by cooling.

Or,

1. The coating material can be gradually applied to core particles tumbling in a vessel rather than being wholly mixed with the core particles from the start of encapsulation.
2. The particles are tumbled in a pan or other device while the coating material is applied slowly.
3. The coating is applied as a solution or as an atomized spray to the desired solid core material in the coating pan.
4. Usually, to remove the coating solvent, warm air is passed over the coated materials as the coatings are being applied in the coating pans. In some cases, final solvent removal is accomplished in drying oven.

2.6.3 Spray Drying

The coating solidification affected by rapid evaporating of solvent in which coating material is dissolved.

Spray Congealing:

The coating solidification is affected by thermally congealing a molten coating material. The removal of solvent is done by sorption, extraction or evaporation technique.

In modern spray dryers the viscosity of the solutions to be sprayed can be as high as 300 mPa.s.

Spray drying and **spray congealing** dispersing the core material in a liquefied coating substance and spraying.

Spray drying is affected by rapid evaporation of a solvent in which the coating material is dissolved.

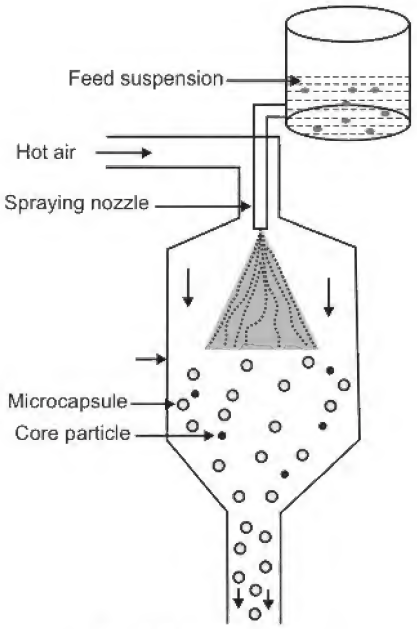


Fig. 2.4: Spray Drying

The equipment components of a standard **spray dryer include:**

1. an air heater
2. atomizer
3. main spray chamber
4. blower or fan
5. cyclone
6. product collector

Microencapsulation by spray-drying is a low-cost commercial process which is mostly used for the encapsulation of fragrances, oils and flavors.

Steps:

1. Core particles are dispersed in a polymer solution and sprayed into a hot chamber.
2. The shell material solidifies onto the core particles as the solvent evaporates.
3. The microcapsules obtained are of polynuclear or matrix type.

Spray congealing can be accomplished with spray drying equipment when the protective coating is applied as a melt.

- Core material is dispersed in a coating material melt rather than a coating solution.
- Coating solidification (and microencapsulation) is accomplished by spraying the hot mixture into a cool air stream. For e.g. microencapsulation of vitamins with digestible waxes for taste masking.

Spray drying is most commonly used in encapsulation method in the food industry. The process is economical and flexible uses equipment that is readily available, and produces particles of good quality.

The process involves three basic steps:

Preparation of a dispersion or emulsion to be processed Homogenization of the dispersion and Atomization of the mass into the drying chamber. Spray dried ingredients typically have a very small particle size (generally less than 100 µm), which makes them highly soluble. Typical shell materials include gum acacia, maltodextrins, hydrophobically modified starch and mixtures. Other polysaccharides like alginate, carboxymethyl cellulose and guar gum. Proteins like whey proteins, soy proteins, sodium caseinate can be used as the wall material in spray drying.

Spray Cooling/Chilling:

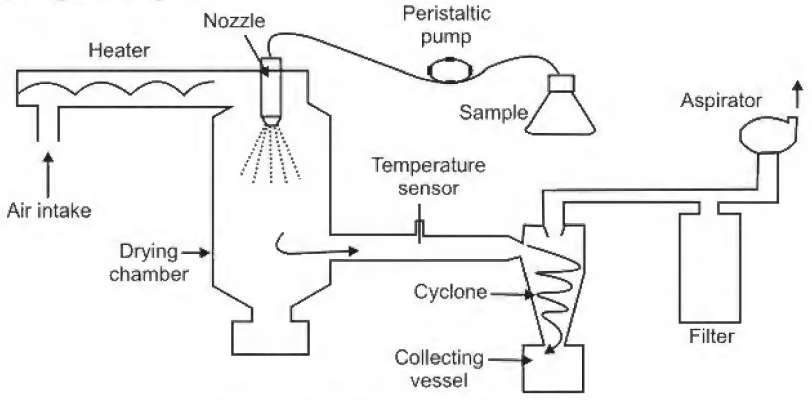


Fig. 2.5: Spray Drying Techniques

Spray drying: Spray = Aqueous solution / Hot air.

Spray congealing: Spray = Hot melt/Cold air.

Spray cooling/chilling is the least expensive encapsulation technology. It is used for the encapsulation of organic and inorganic salts, textural ingredients, enzymes, flavors and other functional ingredients.

It improves heat stability, delay release in wet environments, and/or convert liquid hydrophilic ingredient into free-flowing powders.

Spray cooling/chilling is typically referred to as 'matrix' encapsulation because the particles are more adequately described as aggregates of active ingredient particles buried in the fat matrix.

2.6.4 Coacervation

Coacervation microencapsulation is the phase separation of one or many hydrocolloids from the initial solution and the subsequent deposition of the newly formed coacervate phase around the active ingredient suspended or emulsified in the same reaction media.

Coacervation is a unique microencapsulation technology because of the very high payloads achievable up to 99% and the controlled release possibilities based on mechanical stress, temperature or sustained release.

Coacervation is typically used to encapsulate flavor oil and can also be adapted for the encapsulation of fish oils, nutrients, vitamins, preservatives and enzymes.

There are two methods for coacervation are available, namely simple and complex processes. The mechanism of microcapsule formation for both processes is identical, except for the way in which the phase separation is carried out.

2.6.4.1 Simple Coacervation

A desolvation agent is added for phase separation. Whereas complex coacervation involves complexation between two oppositely charged polymers.

The general process consists of three steps under continuous agitation:

1. Formation of three immiscible chemical phases.
2. Deposition of coating.
3. Rigidization of coating.

Step 1:

Three immiscible phases are as:

(a) Liquid manufacturing vehicle phase.

(b) Core material phase.

(c) Coating material phase.

Coating material phase formed by utilizing following methods:

(a) Temperature change.

(b) By addition of incompatible polymer.

(c) By non-solvent addition.

(d) By salt addition.

(e) Polymer-polymer interaction.

Step 2:

In step 2, the deposition of the liquid polymer around the interface formed between the core material and the liquid vehicle phase. In many cases physical or chemical changes in the coating polymer solution can be induced so that phase separation of the polymer will occur.

Finally the prepared microcapsules are stabilized by crosslinking, desolvation or thermal treatment. Equipment required for microencapsulation; this method is relatively simple; it consists mainly of jacketed tank with variable speed agitator.

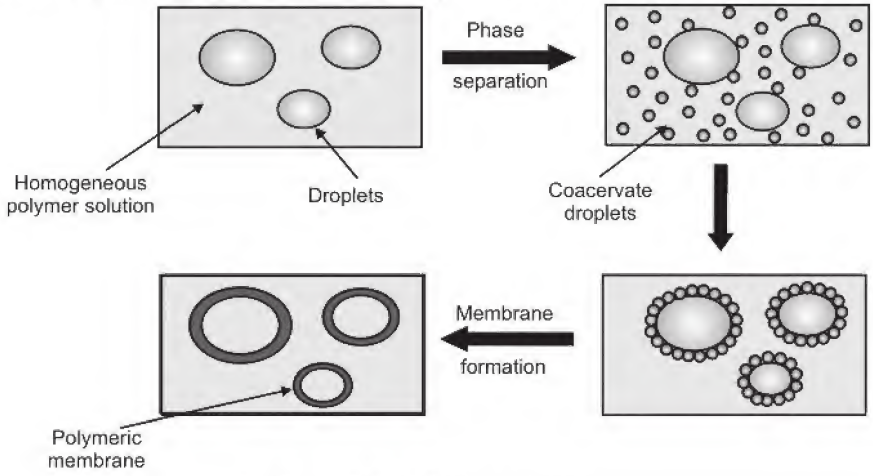


Fig. 2.6: Simple Coacervation

1. Formation of three immiscible phase.
2. Deposition of coating.
3. Rigidization of coating.

2.6.4.2 Complex Coacervation

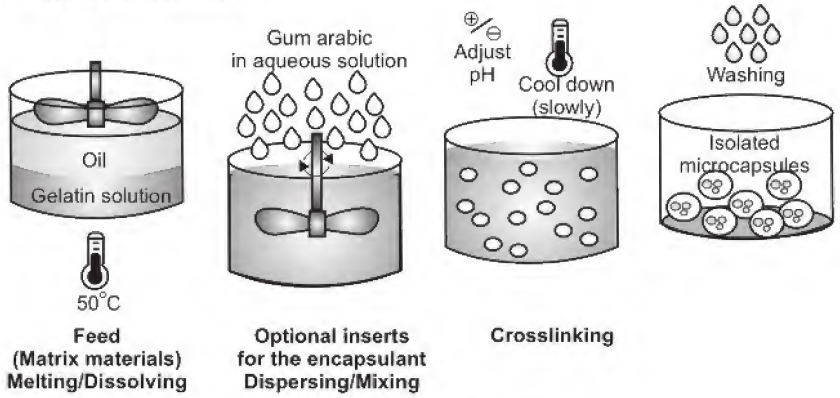


Fig. 2.7: Complex Coacervation

2.6.5 Ionotropic Gelation Technique

In the ionotropic gelation method, polysaccharides (alginate, gellan and pectin) are dissolved in water or in weak acidic medium (chitosan). These solutions are then added drop wise under constant stirring to the solutions containing other counter ions. Due to the complexation between oppositely charged species, polysaccharides undergo ionic gelation and precipitate to form spherical particles. The beads are removed by filtration, washed with distilled water and dried. The method involves an all-aqueous system and avoids residual solvents in microspheres.

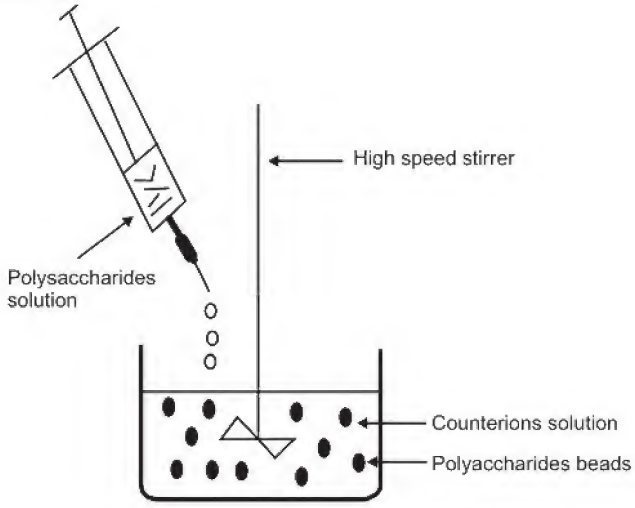


Fig. 2.8: Ionotropic Gelation Technique

2.6.5.1 Schematic Representation of Preparation of Polysaccharides Particles by Ionic Gelation Method

The counterions used for ionotropic gelation can be divided in two major categories:

- Low molecular weight counter ions (e.g. $CaCl_2$, $BaCl_2$, $MgCl_2$, $CuCl_2$, $ZnCl_2$, $CoCl_2$, pyrophosphate, tripolyphosphate, tetrapolyphosphate, octapolyphosphate, hexameta-phosphate and [Fe (CN)6]-4 / [Fe(CN)6]-3).
- High molecular weight ions (e.g. Octyl sulphate, lauryl sulphate, hexadecyl sulphate, cetylstearyl sulphate).

The ionotropic gelation method is very simple and mild. In addition, reversible physical crosslinking by electrostatic interaction instead of chemical crosslinking avoids the possible toxicity of reagents and other undesirable effects.

2.6.6 Solvent Evaporation (Chemical Process)

1. In the case in which the core material is dispersed in the polymer solution, polymer shrinks around the core.
2. In the case in which core material is dissolved in the coating polymer solution, a matrix - type microcapsule is formed.
3. The core materials may be either water - soluble or water - insoluble materials.
4. A variety of film - forming polymers can be used as coatings.

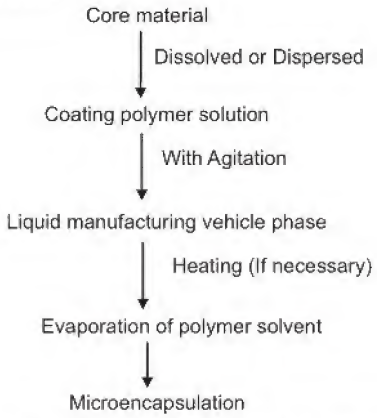


Fig. 2.9: Solvent Evapoation Process

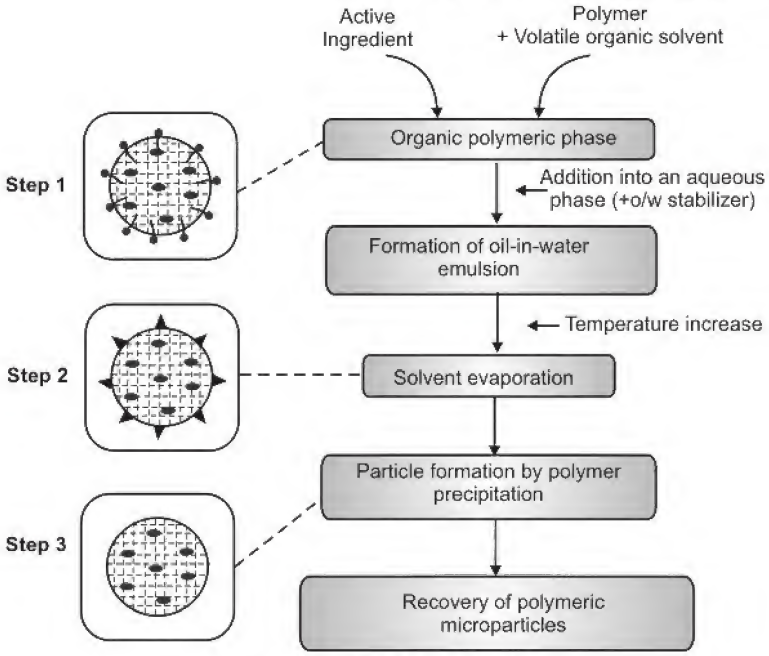


Fig. 2.10: Solvent Evaporation

Step 1:

Formation of a solution/dispersion of the drug into an organic polymer phase.

Step 2:

Emulsification of the polymer phase into an aqueous phase containing a suitable stabilizer, thus, forming a o/w emulsion.

Step 3:

Removal of the organic solvent from the dispersed phase by extraction or evaporation leading to polymer precipitation and formation of the microspheres.

2.6.6.1 Single Emulsion Method

The microparticulate carriers of natural polymers, i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved/ dispersed in aqueous medium followed by dispersion in the non-aqueous medium. For example: oil.

In the 2nd step, cross linking of the dispersed globule is carried out either by means of heat or by using chemical cross linkers. The chemical cross linking agents used – gluteraldehyde, formaldehyde, terephthalate chloride, diacidchloride, etc. Crosslinking by heat is affected by adding the dispersion to previously heated oil. Heat denaturation is not suitable for the thermolabile drugs while the chemical crosslinking suffers disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation.

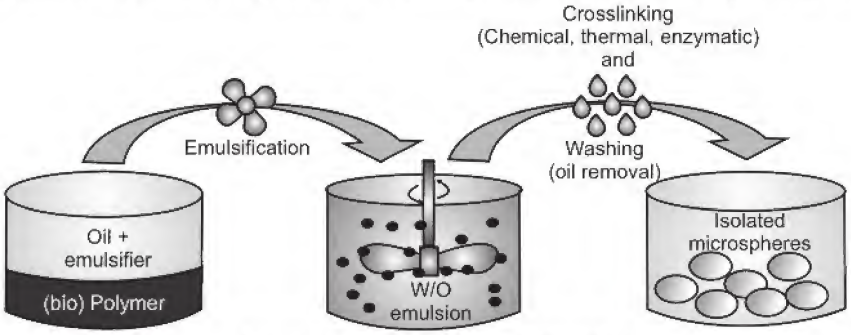


Fig. 2.11: Single Emulsion Method

2.6.6.2 Double Emulsion Method

Involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to the water-soluble drugs, peptides, proteins and the vaccines.

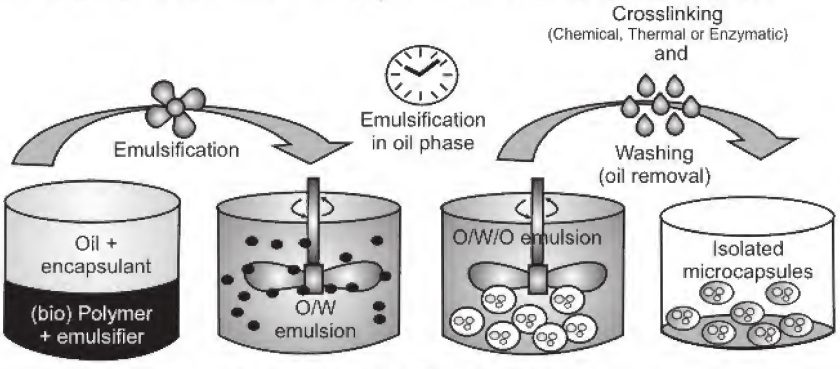


Fig. 2.12: Double Emulsion Method

The aqueous protein solution is dispersed in a lipophilic organic continuous phase which is generally consisted of polymer solution that eventually encapsulates protein contained in dispersed aqueous phase. The primary emulsion is then subjected to the homogenization before addition to aqueous solution of PVA. This results in formation of double emulsion which is then subjected to solvent removal by solvent evaporation maintaining the emulsion at reduced pressure or by stirring so that organic phase evaporates out.

2.6.7 Polymerization

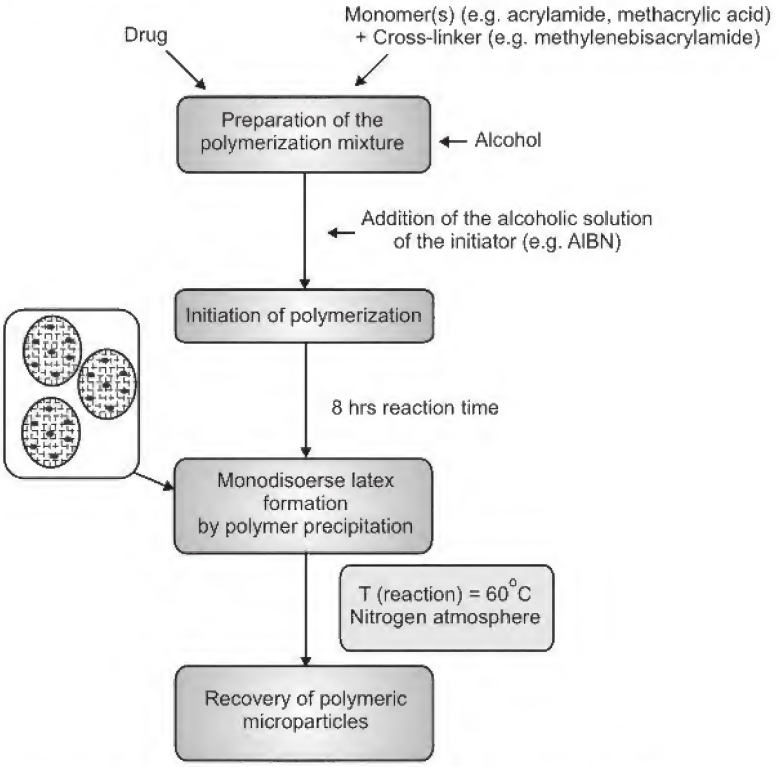
- A relatively new microencapsulation method utilizes polymerization techniques to from protective microcapsule coatings *in situ*.
- The method involves the reaction of monomeric unit located at the interface existing between a core material substance and continuous phase in which the core material is disperse.
- The core material supporting phase is usually a liquid or gas, and therefore polymerization reaction occurs at liquid-liquid, liquid-gas, solid-liquid, or solid-gas interface.

For e.g. in the formation of polyamide (Nylon) polymeric reaction occurring at liquid-liquid interface existing between aliphatic diamine and dicarboxylic acid halide.

1. **Interfacial polymer:** In Interfacial polymerization, the two reactants in a polycondensation meet at an interface and react rapidly.
2. ***In-situ* polymerization:** In a few microencapsulation processes, the direct polymerization of a single monomer is carried out on the particle surface.

   For e.g. Cellulose fibers are encapsulated in polyethylene while immersed in dry toluene. Usual deposition rates are about 0.5μm/min. Coating thickness ranges 0.2-75 μm.
3. **Matrix polymer:** In a number of processes, a core material is imbedded in a polymeric matrix during formation of the particles.

- Prepares microcapsules containing protein solutions by incorporating the protein in the aqueous diamine phase.
- National Lead Corporation - utilizing polymerization techniques.



- Monodisperse microgels in the micron or submicron size range.
- Precipitation polymerization starts from a homogeneous monomer solution in which the synthesized polymer is insoluble.
- The particle size of the resulting microspheres depends on the polymerization conditions, including the monomer/co monomer composition, the amount of initiator and the total monomer concentration.

Fig. 2.13: Polymerization Technique

Table 2.1: Comparison of Interfacial Polymerization and *In-situ* Polymerization

Interfacial polymerization	In-situ polymerization
1. The multifunctional monomer dissolved in liquid core material which will be then dispersed in aqueous phase containing dispersing agent.	1. In this process, no reactive agents are added to the core material.
2. A co-reactant multifunctional amine will be added to the mixture.	2. Polymerization occurs exclusively in the continuous phase and on the continuous phase side of the interface formed by the dispersed core material and continuous phase.

Interfacial polymerization	In-situ polymerization
3. This results in rapid polymerization at interface and generation of capsule shell takes place.	3. Initially a low molecular weight prepolymer will be formed, as time goes on the prepolymer grows in size.
4. A polyuria shell will be formed when isocyanate reacts with amine. Polyanion or polyamide shell will be formed when acid chloride reacts with amine.	4. It deposits on the surface of the dispersed core material thereby generating solid capsule shell.

2.6.8 Multiorific – Centrifugal Process

- The Southwest Research Institute (SWRI) has developed a mechanical process for producing microcapsules that utilizes.
- Centrifugal forces to hurl a core material particle trough an enveloping microencapsulation membrane thereby effecting mechanical microencapsulation.
- Processing variables include; the rotational speed of the cylinder, the flow rate of the core and coating materials, the concentration and viscosity and surface tension of the core material.
- The multiorifice-centrifugal process is capable for microencapsulating liquids and solids of varied size ranges, with diverse coating materials. The encapsulated product can be supplied as slurry in the hardening media or as a dry powder.Production rates of 50 to 75 pounds per our have been achieved with the process.

2.7 APPLICATION OF MICROENCAPSULATION TECHNIQUES

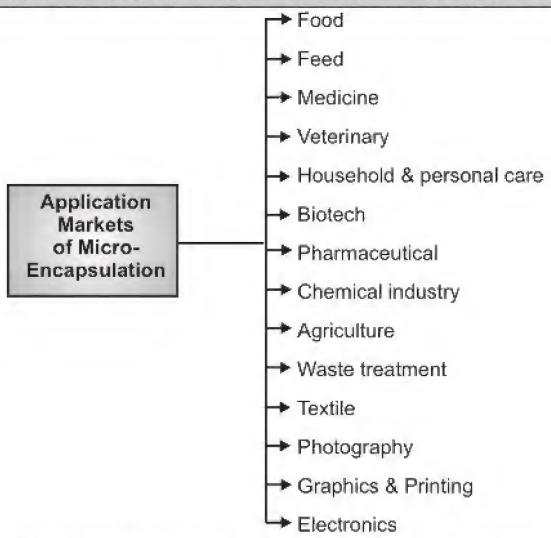


Fig. 2.14: Application of Microencapsulation Techniques

1. **Agricultural Applications:**
   - Reduce insect populations by disrupting their mating process.
   - Protects the pheromone from oxidation and light during storage and release.
2. **Catalysis:**
   - Safe handling, easy recovery, reuse and disposal at an acceptable economic cost.
   - Metal species such as palladium (II) acetate and osmium tetroxide have been encapsulated in polyurea microcapsules and used successfully as recoverable and reusable catalysts without significant leaching and loss of activity.
3. **Food Industry:**
   - Adding ingredients to food products to improve nutritional value can compromise their taste, colour, texture and aroma.
   - Sometimes they slowly degrade and lose their activity, or become hazardous by oxidation reactions.
   - Ingredients can also react with components present in the food system, which may limit bioavailability.
4. **Pharmaceutical Applications:**
   - Potential applications of this drug delivery system are replacement of therapeutic agents (not taken orally today like; insulin), gene therapy and in use of vaccines for treating AIDS, tumors, cancer and diabetes.
   - The delivery of corrective gene sequences in the form of plasmid DNA could provide convenient therapy for a number of genetic diseases such as; cystic fibrosis and hemophilia.

     Lupin has already launched in the market world's first Cephalexin (Ceff-ER) and Cefadroxil (Odoxil OD) antibiotic tablets for treatment of bacterial infections.
   - Aspirin controlled release version ZORprin CR tablets are used for relieving arthritis symptoms.
   - Quinidine gluconate CR tablets are used for treating and preventing abnormal heart rhythms.
   - Niaspan CR tablet is used for improving cholesterol levels and thus reducing the risk for a heart attack.

Some of the applications of microencapsulation can be described in detail as given below:

1. Prolonged release dosage forms.
2. Prepare enteric-coated dosage forms selectively absorbed in the intestine rather than the stomach.
3. It can be used to mask the taste of bitter drugs.

4. To reduce gastric irritation.
5. Used to aid in the addition of oily medicines to tableted dosage forms.
6. To overcome problems inherent in producing tablets from otherwise tacky granulations.
7. To protect drugs from environmental hazards such as; humidity, light, oxygen or heat. For e.g. vitamin A and K have been shown to be protected from moisture and oxygen through microencapsulation.
8. The separations of incompatible substances, for e.g. Pharmaceutical eutectics.

The stability enhancement of incompatible aspirin chlorpheniramine maleate mixture was accomplished by microencapsulating both of them before mixing.

1. To improve the flow properties. e.g. Thiamine, Riboflavin.
2. To enhance the stability. e.g. Vitamins.
3. To reduce the volatility of materials. e.g. Peppermint oil, Methyl salicylate.
4. To avoid incompatibilities. e.g. Aspirin and Chloramphenicol.
5. To mask the unpleasant taste and odour. e.g. Aminophylline, castor oil.
6. To convert liquids into solids. e.g. Castor oil, Eprazinone.
7. To reduce gastric irritation. e.g. Nitrofurantoin, Indomethacin.
8. Microencapsulation has been employed to provide protection to the core materials against atmospheric effects, e.g., Vitamin A Palmitate.
9. Separation of incompatible substance has been achieved by encapsulation.
10. To mask the bitter taste of drugs like Paracetamol, Nitrofurantoin, etc.
11. To reduce gastric and other gastro intestinal (G.I) tract irritations, for e.g. sustained release Aspirin preparations have been reported to cause significantly less G.I. bleeding than conventional preparations.
12. A liquid can be converted to a pseudo-solid for easy handling and storage. For e.g. Eprazinone.
13. Hygroscopic properties of core materials may be reduced by microencapsulation e.g. Sodium chloride.
14. Carbon tetra chlorides and a number of other substances have been microencapsulated to reduce their odour and volatility.
15. To reduce volatility of liquids like peppermint oil.
16. Helps to prepare SRDF and enteric coated products, controlled release products.
17. Used to improve flow properties before compression into tablets.

MUCOADHESIVE DRUG DELIVERY SYSTEM

2.8 MUCOADHESION / BIOADHESION

Mucoadhesive drug delivery system are the systems which utilizes the property of bio adhesion of certain polymers which become adhesive on hydration and can be used for targeting a drug to a particular region of the body for extended periods of time.

The term "mucoadhesion" was coined for the adhesion of the polymers with the surface of the mucosal layer. Bio adhesions are a phenomenon in which two materials at least one of which is biological and are held together by means of interfacial forces. In biological systems, bio adhesion can be classified into 3 types:

1. Adhesion between two biological phases, for example, platelet aggregation and wound healing.
2. Adhesion of a biological phase to an artificial substrate, for example, cell adhesion to culture dishes and bio film formation on prosthetic devices and inserts.
3. Adhesion of an artificial material to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissues and adhesion of sealants to dental enamel.

For drug delivery purposes, the term bio adhesion implies attachment of a drug carrier system to a specified biological location. The biological surface can be epithelial tissue or the mucus coat on the surface of a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion / mucoadhesion as the interaction between a mucin surface and a synthetic or natural polymer. In bio adhesion, the polymer is attached to the biological membrane.

Table 2.2: Composition of Mucous Membrane

Sr. No.	Composition	% Amount
1.	Water	95
2.	Glycoprotein and Lipids	0.5-5.0
3.	Mineral salts	1
4.	Free proteins	0.5-1.0

2.8.1 Advantages of Mucoadhesive Systems

Mucoadhesive systems have three distinct advantages when compared to conventional dosage forms:

1. Readily localized in the region applied to improve and enhance the bioavailability of drugs. For e.g. testosterone and its esters, vasopressin, dopamine, insulin and gentamycin, etc.
2. Facilitate intimate contact of the formulation with underlying absorption surface. This allows modification of tissue permeability for absorption of macromolecules. For e.g. peptides and proteins.
3. Prolong residence time of the dosage form at the site of application and absorption to permit once or twice a day dosing.

2.8.2 Stages of Mucoadhesion

1. Contact Stage
2. Consolidation Stage

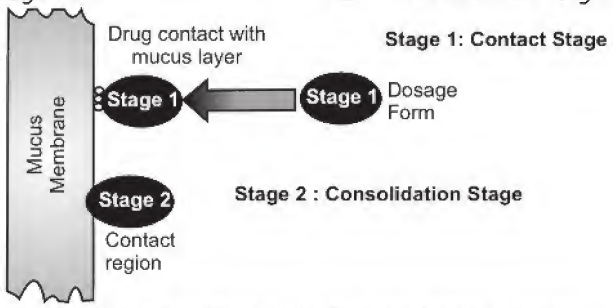


Fig. 2.15: Two Steps of the Mucoadhesion Process

2.8.3 Mechanism of Mucoadhesion

2.8.3.1 Theories of Mucoadhesion

The concept of mucoadhesion is one that has the potential to improve the highly variable residence times experienced by drugs and dosage forms at various sites in the gastrointestinal tract, and consequently, to reduce variability and improve efficacy. Intimate contact with the mucosa should enhance absorption. The mechanisms responsible in the formation of bio adhesive bonds are not fully known. However, most research has described bioadhesive bond formation as a three-step process:

Step 1: Wetting and swelling of polymer.

Step 2: Interpenetration between the polymer chains and the mucosal membrane.

Step 3: Formation of Chemical bonds between the entangled chains.

Step 1: The wetting and swelling step occurs when the polymer spreads over the surface of the biological substrate or mucosal membrane in order to develop an intimate contact with the substrate. This can be readily achieved. For example, by placing a bioadhesive formulation such as; a tablet or paste within the oral cavity or vagina. Bioadhesives are able to adhere to or bond with biological tissues by the help of the surface tension and forces that exist at the site of adsorption or contact. Swelling of polymers occur because the components within the polymers have an affinity for water.

Step 1: The wetting and swelling.

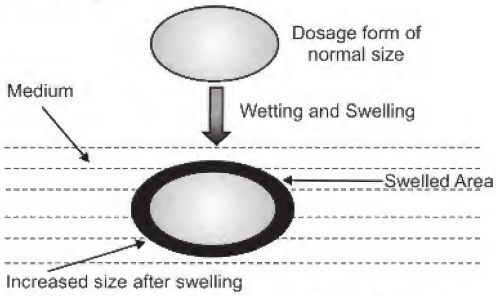


Fig. 2.16: Wetting and Swelling of Polymer

Step 2: The surface of mucosal membranes is composed of high molecular weight polymers known as glycoproteins. In this step, interdiffusion and interpenetration take place between the chains of mucoadhesive polymers and the mucous gel network creating a great area of contact. The strength of these bond depends on the degree of penetration between the two polymer groups. In order to form strong adhesive bonds, one polymer group must be soluble in the other and both polymer types must be of similar chemical structure.

Step 3: In this step, entanglement and formation of weak chemical bonds as well as secondary bonds between the polymer chains mucin molecule. The types of bonding formed between the chains include primary bonds such as covalent bonds and weaker secondary interactions such as van der Waals Interactions and hydrogen bonds. Both primary and secondary bonds are exploited in the manufacture of bioadhesive formulations in which strong adhesions between polymers are formed.

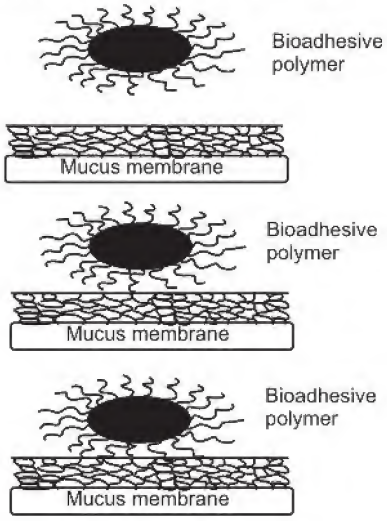


Fig. 2.17: Interdiffusion and Interpenetration of Polymer and Mucus

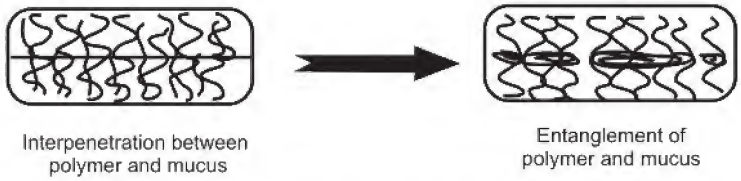


Fig. 2.18: Entanglement of Polymer and Mucus by Chemical Bonds

A complete understanding of how and why certain macromolecules attach to a mucus surface is not yet available, but a few steps involved in the process are generally accepted, at least for solid systems. Several theories have been proposed to explain the fundamental mechanism of adhesion.

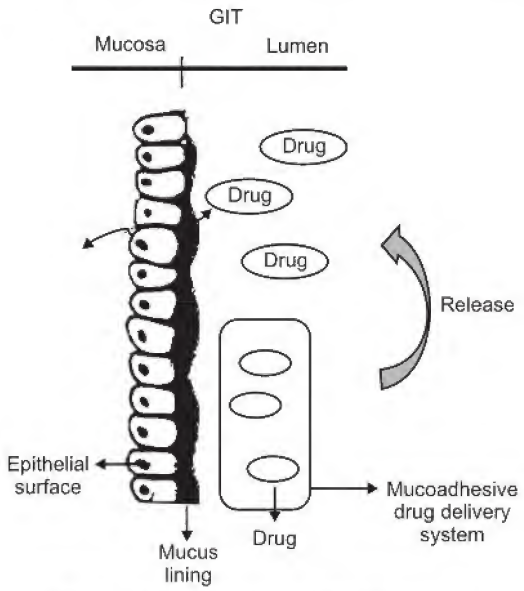


Fig. 2.19: Mechanism of Mucoadhesion

The phenomena of bioadhesion occur by a complex mechanism. Six theories have been proposed, which will explain the mechanism of bioadhesion. The theories are as follows:

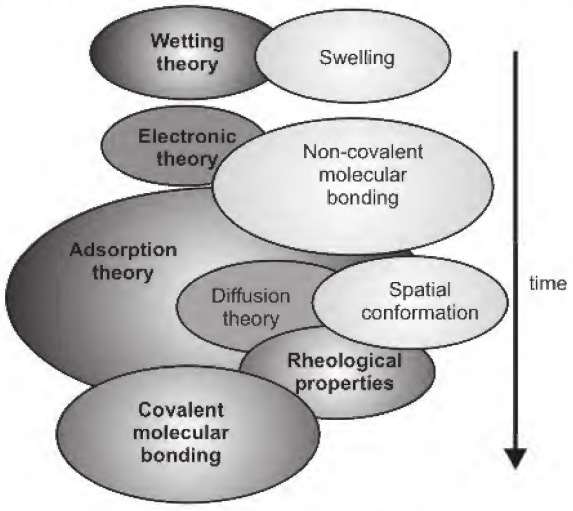


Fig. 2.20: Theory of Mucoadhesion

(a) Electronic theory: Involves the formation of an electric double layer at the mucoadhesive interface by the transfer of electrons between the mucoadhesive polymer and the mucin glycoprotein network. For example: Interaction between positively charged

polymers chitosan and negatively charged mucosal surface which becomes adhesive on hydration and provides an intimate contact between a dosage form and absorbing tissue.

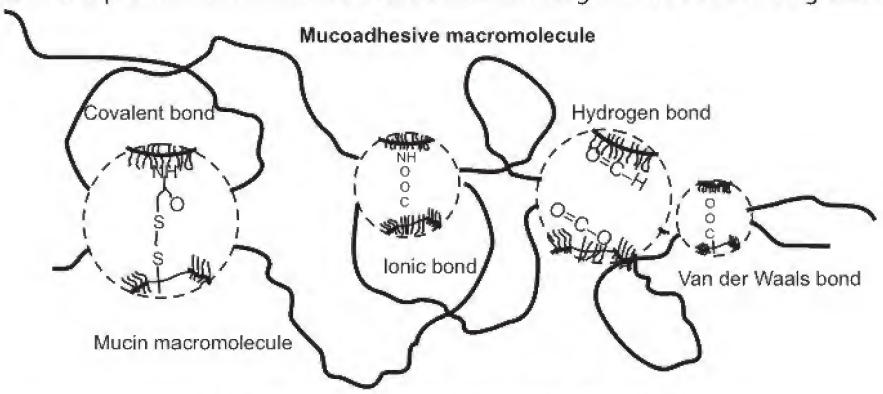


Fig. 2.21: Different Types of Forces for Mucoadhesion

(b) Wetting Theory: States that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface. If two such substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive amongst the substrate surfaces.

(c) Adsorption Theory: According to this theory, after an initial contact between two surfaces, the material adheres because of surface force acting between the atoms in two surfaces. Two types of chemical bonds resulting from these forces can be distinguished as primary chemical bonds of covalent nature and Secondary chemical bonds having many different forces of attraction likes electrostatic forces, Vander Walls forces, hydrogen and hydrophobic bonds.

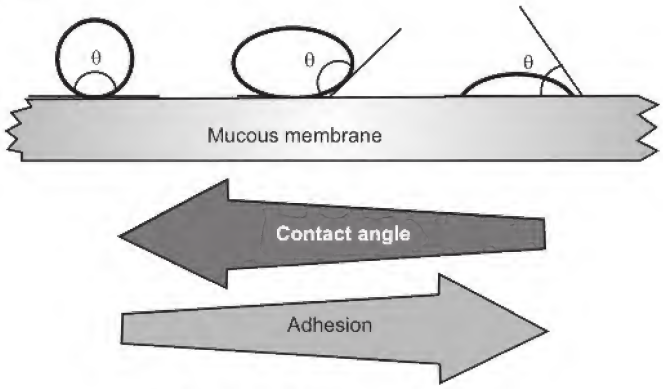


Fig. 2.22: Adsorption Theory

(d) Diffusion Theory: According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi-permanent adhesive bond. The exact depth to which

the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact. The diffusion coefficient in terms depends on the value of molecular weight between cross linking and decreases significantly as the cross linking density increases.

(e) Mechanical Theory: Explains the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the substrate surface thereby forming an interlocked structure which gives rise to adhesion.

(f) Cohesive Theory: Proposes that the phenomena of bio adhesion are mainly due to the intermolecular interactions amongst like-molecules. Based on the above theories, the process of bio adhesion can be broadly classified into two categories.

- Chemical: Electronic and adsorption theories.
- Physical: Wetting, diffusion and cohesive theory.

The process of adhesion may be divided into two stages. During the first stage (also Known as contact stage), wetting of mucoadhesive polymer and mucous membrane occurs followed by the consolidation stage, where the physicochemical interactions take place.

2.8.4 Application of Mucoadhesive Microspheres

- Vaccine delivery for treatment of diseases like; hepatitis, influenza, pertussis, ricin toxoid, diphtheria, birth control. Microsphere in vaccine delivery have a specific advantage like improved antigenicity by adjuvant action, modulation of antigen release, stabilization of antigen.
- Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra-arterial / intravenous application. The concept of targeting i.e. site specific drug delivery is well established because placement of the micro particles in discrete anatomical compartment leads to their retention either because of physical properties of the environment or biophysical interaction of the particles with the cellular content of the target tissue.
- Chemoembolization is an endovascular therapy, which involves the selective arterial embolization of a tumour together with simultaneous or subsequent local delivery the chemotherapeutic agent. The theoretical advantage is that such embolizations will not only provide vascular occlusion but will bring about sustained therapeutic levels of chemotherapeutics in the areas of the tumour. Chemoembolization is an extension of traditional percutaneous embolization techniques.
- **Imaging:** The microspheres have been extensively studied and used for the targeting purposes. Various cells, cell lines, tissues and organs can be imaged using radio labelled microspheres. The particle size range of microspheres is an important factor in determining the imaging of particular sites. The particles injected intravenously apart from the portal vein will become entrapped in the capillary bed of the lungs. This phenomenon is exploited for the scintiographic imaging of the tumour masses in lungs using labelled human serum albumin microspheres.

1. Release of proteins, hormones and peptides over extended period of time.
2. Gene therapy with DNA plasmids and also delivery of insulin.

- **Topical porous microspheres:** Micro sponges are porous microspheres having myriad of interconnected voids of particle size range 5-300 µm. These micro sponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils, etc., are used as the topical carries system.
- **Surface modified microspheres:** Different approaches have been utilized to change the surface properties of carriers to protect them against phagocytic clearance and to alter their body distribution patterns. The most studied surface modifiers are; Antibodies and their fragments, Proteins, Mono-oligo- and polysaccharide, Chelating compounds (EDTA, DTPA or desferroxamine), synthetic soluble polymers. Such modifications are provided surface of microspheres in order to achieve the targeting to the discrete organs.

BUCCAL DELIVERY SYSTEM

2.9 INTRODUCTION

Buccal drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules and increase the residence time of the dosage form at the site of absorption. The drugs which have local action or those which have maximum absorption in gastrointestinal tract (GIT) require increased duration of stay in GIT. Thus, buccal dosage forms are advantageous in increasing the drug plasma concentrations and also therapeutic activity.

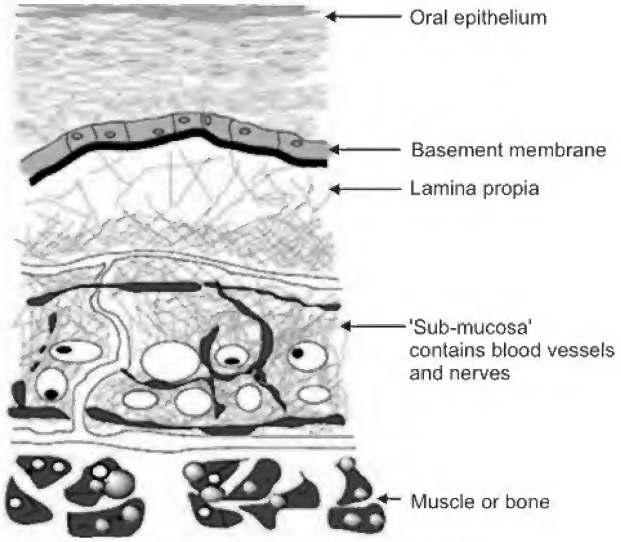


Fig. 2.23: Structure of Human Oral Mucosa

2.9.1 Oral Epithelium

The epithelium of the mouth consists of stratified, squamous epithelium, which can be keratinized, or nonkeratinized. It contains following layers: Stratum distendum Stratum filamentosum Stratum suprabasale, Stratum basale.

Lamina Propria: Constitutes of a continuous sheet of connective tissue containing collagen, elastic fibers and cellular components in a hydrated ground substance. It also carries blood capillaries and nerve fibers that serve the mucosa. It is through the blood vessels in the lamina propria that drug moieties can gain entry to the systemic circulation.

Submucosa: This is a layer of loose connective tissue that supports the epithelium and also contains blood vessels, lymphatics and nerves.

2.9.2 Formulation Design

Pharmaceutical considerations: Great care needs to be exercised while developing a safe and effective buccal adhesive drug delivery device. Factors influencing drug release and penetration through buccal mucosa are organoleptic factors and effects of additives used to improve drug release pattern and absorption, the effects of local drug irritation caused at the site of application are to be considered while designing a formulation.

2.9.2.1 Physiological Considerations

Physiological considerations such as; texture of buccal mucosa, thickness of the mucus layer, its turn over time, effect of saliva and other environmental factors are to be considered in designing the dosage forms.

For e.g. Saliva contains moderate levels of esterases, carbohydrases, and phosphatases that may degrade certain drugs. Although saliva secretion facilitates the dissolution of drug, involuntary swallowing of saliva also affects its bioavailability

2.9.2.2 Pharmacological Considerations

Drug absorption depends on the partition coefficient of the drugs. Generally, lipophilic drugs absorb through the transcellular route, whereas; hydrophilic drugs absorb through the paracellular route. Chemical modification may increase drug penetration through buccal mucosa. Residence time and local concentration of the drug in the mucosa, the amount of drug transported across the mucosa into the blood are the responsible factors for local or systemic drug delivery. Optimization by a suitable formulation design fastens drug release from the dosage form and taken up by the oral mucosa.

2.9.3 Basic Components for BDDS

Buccal adhesive drug delivery systems with the size 1–3 sq.cm and a daily dose of 25 mg or less are preferable. The maximal duration of buccal delivery is approximately 4–6 hrs. To make such dosage form following components are required:

2.9.3.1 Bioadhesive Polymers

Bioadhesive formulations use polymers as the adhesive component. These formulations are often water soluble and when in a dry form attract water from the biological surface and this water transfer leads to a strong interaction. It also forms viscous liquids when hydrated

with water that increases their retention time over mucosal surfaces and may lead to adhesive interactions. They should possess certain physicochemical features including hydrophilicity, numerous hydrogen bond-forming groups, and flexibility for interpenetration with mucus and epithelial tissue, and visco-elastic properties.

2.9.3.2 Polymers in Buccal Drug Delivery

Polymers remain the most versatile class of biomaterials, beingextensively applied in medicine and biotechnology as well as in the food and cosmetic industries. Applications include surgical devices, implants and supporting materials (for e.g. artificial organs, prostheses and sutures), drug–delivery systems with different routes of administration and design, carriers of immobilized enzymes and cells, biosensors, components of diagnostic assays, bioadhesives, ocular devices, and materials for orthopedic applications.

Classifying the properties of polymers for their selection as biomaterials is challenging, because a wide variety of materials are available for a particular application (e.g. surgery, drug delivery) and no single, simple set of methods can be used to characterize polymers.

Polymers used as biomaterials can be naturally occurring, synthetic or a combination of both. Polymers that adhere to themucin-epithelial surface can be conveniently divided into three broad categories:

- Polymers that become sticky when placed in water and owe their bioadhesion to stickiness.
- Polymers that adhere through non-specific, non-covalent interactions, which are primarily electrostatic in nature.
- Polymers that bind to specific receptor sites on the cell surface.

2.9.3.3 Characteristics of an Ideal Polymer for Mucoadhesive Drug Delivery System

An ideal polymer should possess the following characteristics:

- The polymer and its degradation products should be non-toxic and non-absorbable from the GI tract.
- It should be non-irritant to the mucous membrane.
- It should preferably form a strong non-covalent bond with mucin-epithelial cell surfaces.
- It should preferably adhere quickly to moist tissue and should possess some site specificity.
- It should allow easy incorporation of the drug and offer no hindrance to its release.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The cost of the polymer should not be high so that the prepared dosage form remains competitive.

Table 2.3: Categories of Polymers According to the Criteria

Criteria	Categories	Examples
Source	Semi-natural/ natural	Agarose, chitosan, gelatin Hyaluronic acid. Various gums (guar, haken, xanthan, gellan, carrageenan, pectin.
	Synthetic	**Cellulose derivatives** (CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, methyl hydroxyethyl cellulose] **Poly(acrylic acid)-based polymers.** (CP, PC, PAA polyacrylates, methacrylic acid), poly poly(acrylic acid-co-ethylhexylacrylate), poly (methacrylate), poly (alkylcyanoacrylate), poly (isohexyl cyanoacrylate), poly (isobutyl cyanoacrylate), copolymer of acrylic acid and PEG). **Others:** Poly PHPMAm), polyoxyethylene, PVA. PVP, thiolated polymers.
Aqueous solubility	Water-soluble	CP, HEC, HPC (Waterb38 8C), HPMC (cold water). PAA, sodium CMC, sodium alginate.
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC.
Charge	Cationic	Amino Dextran, chitosan. (DEAE)-dextran, TMC.
	Anionic	Chitosan-EDTA, CP, CMC pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum.
	Non-ionic	Hydroxyethyl starch. HPC polyethylene oxide), PVA, PVP, scleroglucan.
Potential Bioadhesives forces	Covalent	Cyanoacrylate.
	Hydrogen bond	Acrylates [hydroxylated methacrylate, poly(methacrylic acid)], CP, PC, PVA.
	Electrostatic interaction	Chitosan

2.9.3.4 Permeation Enhancer

Membrane permeation is the limiting factor for many drugs in the development of buccal adhesive delivery devices. The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. As most of the penetration enhancers were originally designed for purposes other than absorption enhancement, a systemic search for

safe and effective penetration enhancers must be a priority in drug delivery. The goal of designing penetration enhancers, with improved efficacy and reduced toxicity profile is possible by understanding the relationship between enhancer structure and the effect induced in the membrane and of course, the mechanism of action. However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. In some cases, usage of enhancers in combination has shown synergistic effect than the individual enhancers. The efficacy of enhancer in one site is not same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties. Penetration enhancement to the buccal membrane is drug specific. Effective penetration enhancers for transdermal or intestinal drug delivery may not have similar effects on buccal drug delivery because of structural differences; however, enhancers used to improve drug permeation in other absorptive mucosae improve drug penetration through buccal mucosa. These permeation enhancers should be safe and nontoxic, pharmacologically and chemically inert, non-irritant, and non-allergenic.

Example: Cyclodextrin, benzalkonium chloride, dextran sulfate, lauric acid, menthol, sodium EDTA, sodium salicylate

2.9.3.5 Drug of Choice (API)

- Choice of drug for buccal formulation is property specific.
- Molecular weight of 1000 Dalton or less.
- Should possess lipophilic and hydrophilic properties.
- Should have low melting point Biological properties.
- Should be potent.
- $T_{1/2}$ should be shorter.
- Nonirritant to oral mucosa.
- Drug degraded in GI tract.

2.9.4 Buccal Mucoadhesive Dosage Forms

Buccal mucoadhesive dosage forms can be categorized into three types based on their geometry:

Type I:

It is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing.

Type II:

It is a device in which an impermeable backing layer is superimposed on top of the drug loaded bioadhesive layer, creating a double-layered device and preventing drug loss from the top surface into the oral cavity.

Type III:

It is a unidirectional drug release device, from which drug loss is minimal, since the drug is released only from the side adjacent to the buccal mucosa. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa.

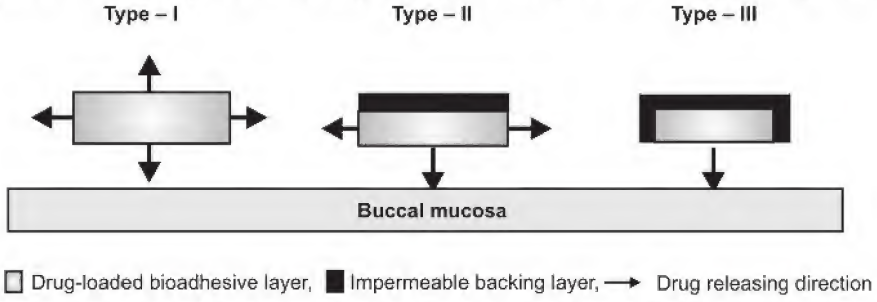


Fig. 2.24: Classification Buccal Adhesive Dosage Form

Buccal adhesive dosage forms are broadly classified in following dosage forms:

- Solid buccal adhesive dosage forms.
- Semi-solid buccal adhesive dosage forms.
- Liquid buccal adhesive dosage forms.

2.9.4.1 Solid Forms

Several solid lozenges formulations have been developed and are commercially available, including nitroglycerin sublingual tablet, fentanyl lozenge on a handle and prochlorperazine buccal tablets. Although these formulations vary in shape and size, they share many common characteristics. This method of delivery is simple for patients to use. The solid formulations dissolve in the oral cavity. The drugs are released and exposed to the entire mucosa and the top third of the esophageal mucosa. The limitation of this delivery form is the short residence time. Depending on the size and formulation, the lozenge or tablet is usually dissolved within 30 min, thus limiting the total amount of drug that can be delivered. The dissolution or disintegration is usually controlled by the patient, i.e. how hard they suck the unit. Increased sucking and saliva production causes swallowing and loss of drug down the esophagus and the gastrointestinal tract. Thus, solid dosage forms generally have a much higher inter- and intraindividual variation in absorption and bioavailability. In addition, since these formulations are open systems, the delivery medium is not well controlled. Although the formulation offers some control, Oral transmucosal technology. Difficult to control drug or other ingredient concentrations because the media is constantly diluted by saliva. This makes it difficult to effectively use permeation enhancers in this type of system. Taste of the drug is another hurdle for this delivery system. Unless the drug is tasteless or the taste can be masked by sweetening and flavorings agents, it is difficult to achieve high patient acceptability of this type of product.

2.9.4.2 Semi-Solid Dosage Form

(a) Gum:

Chewing gum is one of the modern approaches to oral transmucosal drug delivery and is a useful means for systemic drug delivery. The advantages of chewing gum over other oral mucosal drug delivery systems are the possibility of controlled drug release over an extended time and the potential to improve the variability in drug release and retention times. One of the advantages of chewing gum is convenience. Furthermore, an individual may be able to control the drug intake by simply changing the rate and vigor of chewing, or expelling the gum altogether. Since chewing gum is also an open system, it shares many of the same limitations of the other solid formulations.

(b) Patches:

Flexible adhesive patches have been developed in an effort to overcome some of the drawbacks of other dosage forms. Transmucosal delivery patches have unique characteristics, including relatively rapid onset of drug delivery, sustained drug release and rapid decline in the serum drug concentration when the patch is removed. Also, a buccal patch is confined to the buccal area over which it is attached and therefore the absorption profile may have less inter- and intraindividual variability. In general, oral mucosal patches can be classified into three categories: patches with a dissolvable matrix, patches with a non-dissolvable backing, and patches with a dissolvable backing. Patches with a dissolvable matrix are designed to release drug into the oral cavity. They work similarly to, and share many of the limitations of, the solid dos e form. The mucoadhesive layer, either in the drug matrix or attached to drug matrix as an additional layer, prolongs the duration of drug matrix in the oral cavity. Therefore, compared with other open dosage forms, these types of patches are longer acting and can potentially deliver more drugs. They also use the entire oral cavity mucosa as compared with other closed systems that typically use smaller areas. These types of patches are also suitable for treating local diseases such as candidiasis or mucositis. Patches with non- dissolvable backing are usually designed for systemic delivery. Since they are closed systems and the formulations are protected from saliva, the drug concentrations are controlled and drug is continuously delivered for 10 to 15 h. The disadvantages of these systems are that they use only a small mucosal area and the backings have to be removed by the patient after drug administration. Patches with dissolvable backing share many characteristics of patches with non-dissolvable backing, but they have the advantage of the entire patch dissolving in the oral cavity. Patches with dissolvable backings are shorter acting than patches with non-dissolvable backing. Oral mucosal dosage forms are convenient, easy to use, and have the potential to offer a low-cost and painless alternative to more invasive routes of administration. Each delivery form offers very distinct delivery characteristics that can be used in a broad range of therapies. The majority of patches provide a longer period over which to deliver the formulated as either solvent cast mucoadhesive polymer discs or drug to and through the buccal mucosa.

2.9.4.3 Gel-forming liquids and *in situ* gel

Viscous liquids have been investigated primarily to coat the mucosa to act as a protectant or a vehicle for drug delivery for the treatment of local disorders, including motility dysfunction, fungal infections. Using sodium alginate suspension as a novel bioadhesive liquid, researchers showed that the esophageal surface can be coated to protect against reflux and can deliver therapeutic agents to the damaged mucosa. The retention behavior of various bioadhesive formulations was evaluated on the esophageal surface under conditions mimicking the salivary flow. Both polycarbophil and xanthum gum demonstrated excellent bioadhesive potential, and carmellose sodium and theromo-sensitive poloxamer (Lutrol 407) demonstrated poor retention. A thermosensitive hydrogel of poloxamer covalently linked to polyacrylic acid and carbopol. This "esophageal bandage", upon oral administration, demonstrated significant retention within the esophagus

IMPLANTABLE DRUG DELIVERY SYSTEM

2.10 INTRODUCTION

In the year 1861, Lafarge introduced the concept of implantable system for sustained release drug administration. In the very beginning, it was first introduced to produce the solid implants containing steroid hormones implantable system for long term delivery.

Implantable drug delivery systems are placed under the skin and designed to release drugs into the bloodstream without the repeat insertion of needles.

"A sterile drug delivery device for subcutaneous implantation having the ability to deliver the drugs at a controlled rate over a prolonged period of time, comprising a rod shaped polymeric inner matrix with an elongated body and two ends."

2.10.1 Ideal Properties of an Implantable Drug Delivery System

- Environmentally stable.
- Biocompatible.
- Easy to sterilize.
- Rate controlled release of drug.
- Improve patient compliance by reducing the frequency of the drug administration over the entire period of treatment.
- Easy to manufacture and relatively inexpensive.
- Good mechanical strength.
- Free from surgical procedure.

2.10.2 Advantages of an Implantable Drug Delivery System

Convenience: Implantation therapy permits patients to receive medication outside the hospital with minimal medical surveillance.

Compliance: Compliance is increased greatly by allowing a reduction or complete elimination of patient involved dosing.

Improved drug delivery: Using an implantable drug delivery system the drug is delivered locally or systemic circulation with minimal interference by biological or metabolic barriers.

Potential for controlled release: These deliver drugs by zero order-controlled release kinetics, so it can reduce the dosage frequency and increase the patient compliance.

Potential for intermittent release: Extremely programmable pumps can facilitate intermittent release in response to various factors such as; cardiac rhythm, metabolic needs, etc.

Flexibility: Various types of flexibilities like; materials, method of manufactures, etc. are available in case of implants. Controlled delivery of both hydrophilic and lipophilic drugs can be obtained from here.

2.10.3 Disadvantages of an Implantable Drug Delivery System

Invasive: For the insertion of the implants, patient has to face either a major or a minor surgical procedure.

Termination: Non-biodegradable polymeric implants can be terminated from the body also with the help of a surgical method at the end of the treatment.

Danger of device failure: If due to some reason, the device fails to operate properly during the treatment then again surgical steps should be taken for removal of the device from the patient's body.

Limited to potent drug: The size of the device is very small to reduce the patient's discomfort, therefore only the potent drugs which are very small in amount can only be used in this system.

Adverse reaction: As a high concentration of drug is delivered to the implantation site with the help of the device therefore there is always a chance of adverse reaction due to this local high concentration.

2.10.4 Mechanism of Drug Release from Implantable Therapeutic System

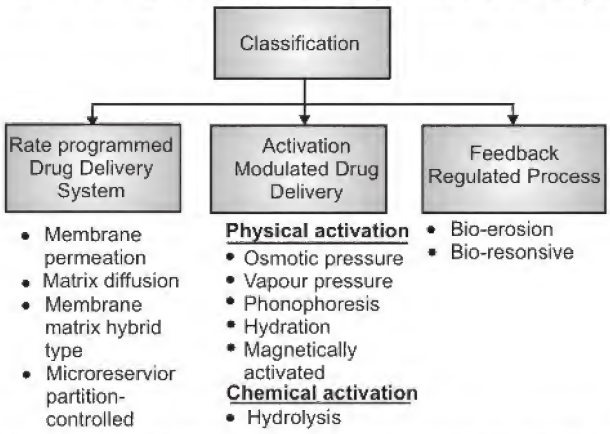


Fig. 2.25: Classification of Drug Release from Implantable Therapeutic System

A. Polymer Membrane Permeation-Controlled Drug Delivery System:

- In this controlled drug delivery device, drug reservoir is totally encapsulated within a capsule shaped or spherical compartment.
- This total system is covered with a rate controlling polymeric membrane.
- The drug reservoir can be either solid particles or the dispersion of the solid particles in a liquid or solid dispersing medium.
- The encapsulation of the drug reservoir system inside the polymeric membrane can be done by the encapsulation, microencapsulation, molding, extrusion, etc.

Fig. 2.26: Norplant Subdermal Implant

B. Polymer Matrix Diffusion-Controlled Drug Delivery System:

- In this implantable device, the reservoir is formed by dispersion of the solid particles throughout a lipophilic or hydrophilic polymer matrix.
- This dispersion can be obtained by dispersing the solid drug dosage form in the liquid or semisolid polymer matrix at the room temperature followed by cross linking of the polymer chains.
- The drug polymer dispersions are then molded or extruded to form drug delivery devices of various shapes.
- It can also be prepared by dissolving the drug solid or the polymer in an organic solvent followed by conservation or solid evaporation at an elevated temperature under a vacuum to form microsphere.

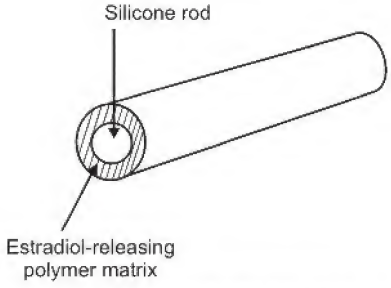


Fig. 2.27: Compudose Implant

C. Membrane-Matrix Hybrid Type Drug Delivery System:

- This type of drug delivery system is actually a hybrid form of polymer membrane permeation-controlled drug delivery system and the polymer matrix permeation-controlled drug delivery system.
- It follows the constant drug release kinetics just like the polymer membrane permeation-controlled drug delivery system.
- Therefore, it will reduce the chances of dose dumping from the reservoir compartment.

- Just like the matrix diffusion system, the drug reservoir is also prepared by the homogeneous dispersion of the drug solid particles throughout a polymer matrix.
- But in case of this implantable drug delivery, the total reservoir is encapsulated within a rate controlling polymeric membrane.
- This is actually a sandwich type implantable device.

Fig. 2.28: Norplant II Subdermal Implant

D. Micro Reservoir Partition-Controlled Drug Delivery System:

- In this controlled release drug delivery device, the drug reservoir is a suspension of drug crystals in an aqueous solution of water miscible polymer and it also forms a homogeneous dispersion.
- Micro dispersion is obtained by the high energy dispersion technique.
- Different size and shapes of drug delivery devices can be obtained with the help of extrusion and molding.
- According to the physicochemical properties of the drug, the device can be further coated with a layer of biocompatible polymer to modify the mechanism and the rate of drug release.

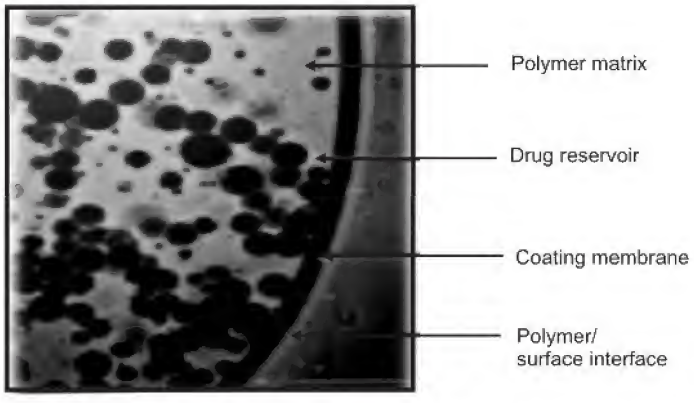


Fig. 2.29: Syncromate Implant

E. Osmotic Pressure Activated Drug Delivery System:

1. From the above-mentioned definition, it can be easily assumed that the osmotic pressure is the main source of energy in this case to activate and modulate the delivery of drug.
2. In here, the drug reservoir is either a solution or a semisolid state which is contained within a semipermeable compartment with controlled water permeability.
3. The volume of the drug solution released is determined by the equation.

$$\frac{dv}{dt} = \frac{P_{\infty}A_{\infty}}{h_{\infty}} [\sigma (\pi_1 - \pi_2) - (P_1 - P_2)]$$

In this type of controlled drug delivery system, the release of the drug takes place due to osmotic pressure.

- Drug reservoir which can be either a solid or a suspension is contained in a semipermeable housing.
- The release is activated through a specially formed orifice and rate of release is modulated by controlling the osmotic gradient.
- Thus, release rate is dependent on water permeability of membrane, solubility of osmogen, effective surface area of semi-permiable housing as well as osmotic gradient.
- Representative example of this type of implantable controlled release drug delivery system is alzet osmotic pump.

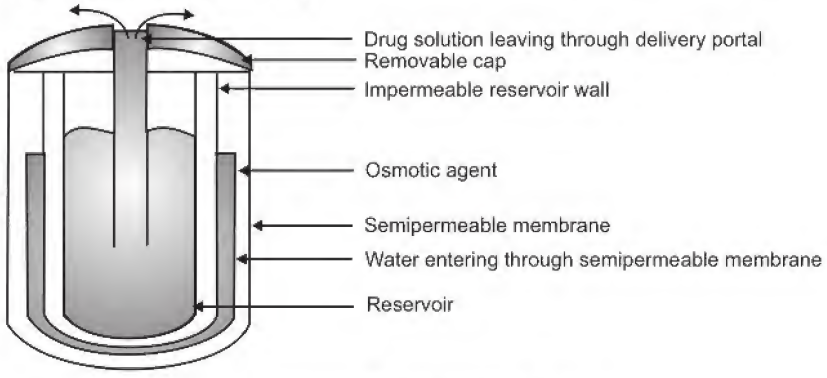


Fig. 2.30: Alzet Osmotic Pump

F. Higuchi Leeper Osmotic Pumps:

The Higuchi-Leeper pump has no water chamber, and the activation of the device occurs after imbibition of the water from the surrounding environment. This variation allows the

device to be prepared loaded with drug and can be stored for long prior to use. Higuchi-Leeper pumps contain a rigid housing and a semi-permeable membrane supported on a perforated frame; a salt chamber containing a fluid solution with an excess of solid salt is usually present in this type of pump. Upon administration/implantation, surrounding biological fluid penetrates into the device through porous and semi-permeable membrane and dissolves the $MgSO_4$, creating osmotic pressure inside the device that pushes movable separator toward the drug chamber to remove drug outside the device. It is widely employed for veterinary use. This type of pump is implanted in body of an animal for delivery of antibiotics or growth hormones to animals

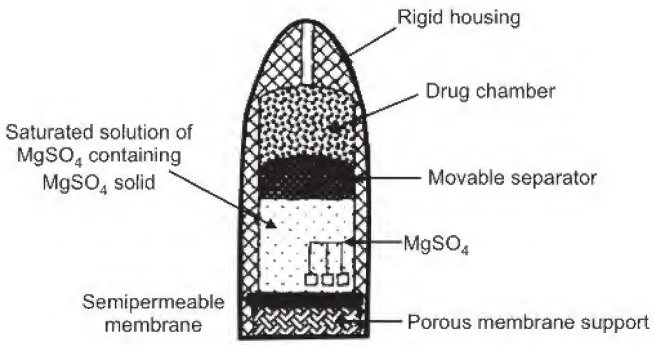


Fig. 2.31: Higuchi Leeper Osmotic Pump

G. Higuchi-Theeuwes Osmotic Pump:

In this device, the rigid housing consisted of a semi-permeable membrane. This membrane is strong enough to withstand the pumping pressure developed inside the device due to imbibition of water. The drug is loaded in the device only prior to its application, which extends advantage for storage of the device for longer duration. The release of the drug from the device is governed by the salt used in the salt chamber and the permeability characteristics of the outer membrane.

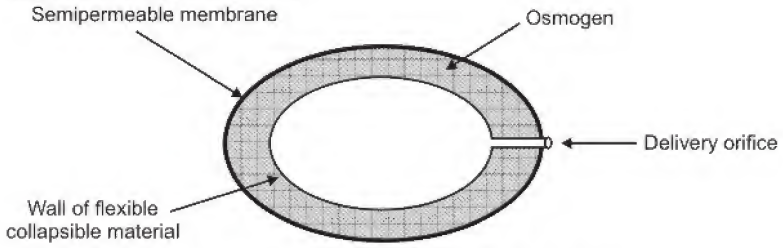


Fig. 2.32: Higuchi-Theeuwes Osmotic Pump

H. Elementary Osmotic Pump (EOP):

It is fabricated as a tablet coated with semi permeable membrane, usually cellulose acetate. A small orifice is drilled through the membrane coating. When this coated tablet is exposed to an aqueous environment, the osmotic pressure of the soluble drug inside the tablet draws water through the semi permeable coating and a saturated aqueous solution of drug is formed inside the device. The membrane is non-extensible and the increase in volume due to imbibition of water raises the hydrostatic pressure inside the tablet, eventually leading to flow of saturated solution of active agent out of the device through a small orifice.

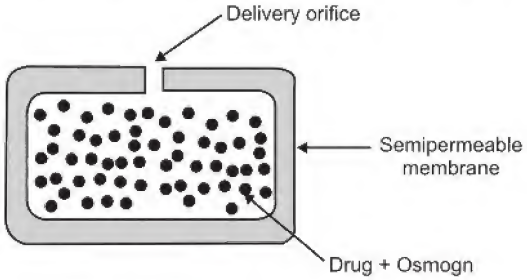


Fig. 2.33: Elementary Osmotic Pump

I. Push-Pull Osmotic Pump (PPOP):

Push-pull osmotic pump is delivered both poorly water soluble and highly water-soluble drugs at a constant rate. This system resembles a standard bilayer coated tablet. One layer (the upper layer) contains drug in a formulation of polymeric, osmotic agent, and other tablet excipients. This polymeric osmotic agent has the ability to form a suspension of drug *in situ*. When this tablet later imbibes water, the other layer contains osmotic and coloring agents, polymer and tablet excipients. These layers are formed and bonded together by tablet compression to form a single bilayer core. The tablet core is then coated with semi-permeable membrane. After the coating has been applied, a small hole is drilled through the membrane by a laser or mechanical drill on the drug layer side of the tablet. When the system is placed in aqueous environment, water is attracted into the tablet by an osmotic agent in both the layers. The osmotic attraction in the drug layer pulls water into the compartment to form *in situ* a suspension of drug. The osmotic agent in the nondrug layer simultaneously attracts water into that compartment, causing it to expand volumetrically, and the expansion of non-drug layer pushes the drug suspension out of the delivery orifice.

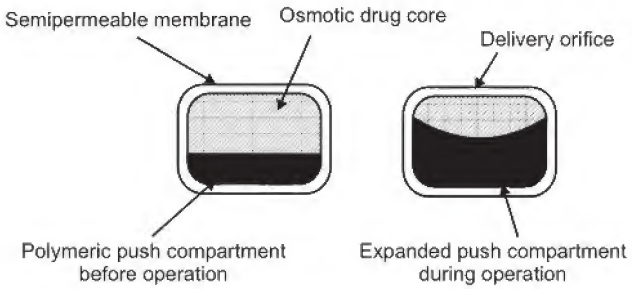


Fig. 2.34: Push Pull Osmotic Pump

J. Controlled Porosity Osmotic Pump (CPOP):

It is an osmotic tablet wherein the delivery orifices (holes) are formed *in situ* through leaching of water-soluble pore-forming agents incorporated in semi-permeable membrane (SPM) (e.g., urea, nicotinamide, sorbitol, etc.). Drug release rate from CPOP depends on various factors like; coating thickness, solubility of drug in tablet core, level of leachable pore-forming agent(s) and the osmotic pressure difference across the membrane.

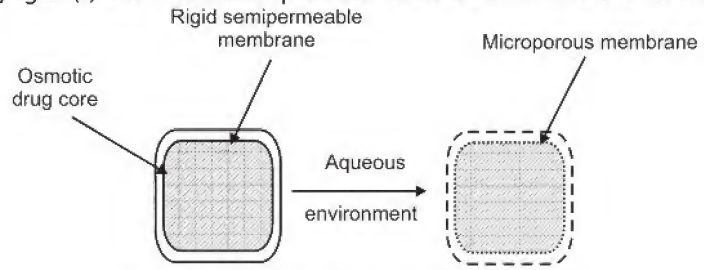


Fig. 2.35: Controlled Porosity Osmotic Pump

K. Liquid-Oral Osmotic (L-OROS) System:

Various L-OROS systems available to provide controlled delivery of liquid drug formulations include; L-OROS hardcap, L-OROS softcap, and a delayed liquid bolus delivery system. Each of these systems includes; a liquid drug layer, an osmotic engine or push layer, and a semi-permeable membrane coating. When the system is in contact with the aqueous environment, water permeates across the rate-controlling membrane and activates the osmotic layer.

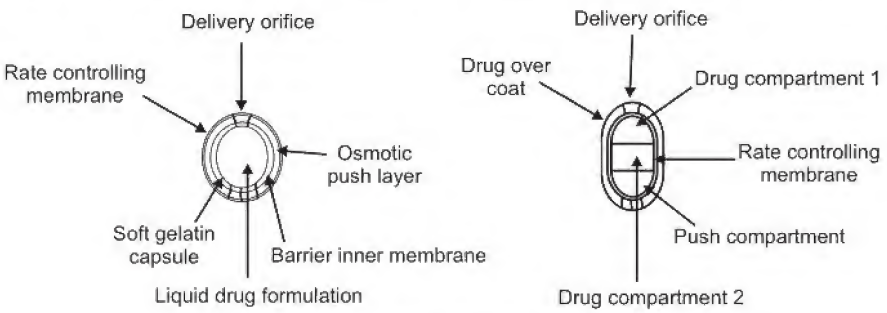


Fig. 2.36: Liquid Oral Osmotic System

The delayed liquid bolus delivery system comprises of three layers: a placebo delay layer, a liquid drug layer, and an osmotic engine, all surrounded by a rate-controlling semi-permeable membrane (SPM). The delivery orifice is drilled on the placebo layer end of the capsule shaped device. When the osmotic engine expands, the placebo is released first, delaying release of the drug layer. Drug release can be delayed from 1 to 10 hours, depending on permeability of the rate-controlling membrane and the size of placebo.

L. Sandwiched Osmotic Tablet (SOT):

The sandwiched osmotic tablet is composed of polymeric push layer sandwiched between two drug layers with two delivery orifices. When placed in the aqueous environment, the middle push layer containing the swelling agents swells and the drug is released from the two orifices situated on opposite sides of the tablet; thus, sandwiched osmotic tablets (SOTS) can be suitable for drugs prone to cause local irritation of the gastric mucosa.

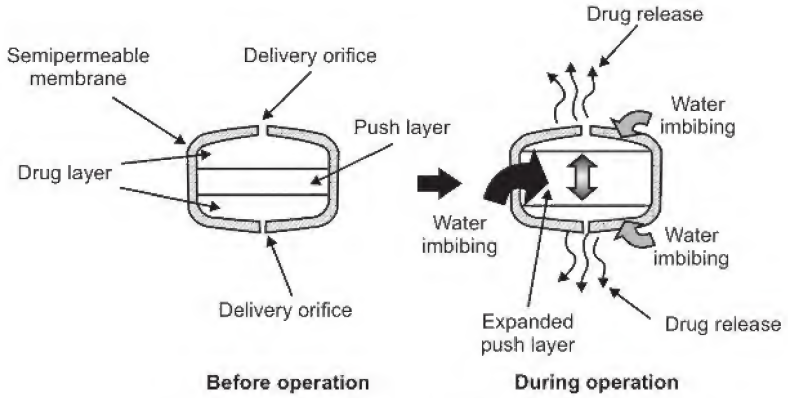


Fig. 2.37: Sandwiched Osmotic Tablet

QUESTIONS

1. Define microencapsulation. List out the advantages and disadvantages of microencapsulation.
2. Explain the techniques of microencapsulation.
3. Explain the coacervation phase separation technique of microencapsulation.
4. Explain the Singer-Nicolson model for the mucosal membrane.
5. Explain the theories of mucoadhesion.
6. Write a short note on mucoadhesive polymers.
7. Explain various routes of transmucosal permeation.
8. What are the mechanisms and pathways for trans-mucosal permeation of drugs?
9. Enlist the advantages and disadvantages of buccal drug delivery.
10. List the ideal requirements of suitable drug candidates for buccal delivery.
11. Explain the approaches used in the design of mucoadhesive buccal DDS.
12. Classify and explain the design of buccal dosage forms.
13. Define implantable drug delivery system and how they are developed.
14. List out the advantages and disadvantages of Implantable Drug Delivery Systems.
15. Explain about different type of implants.
16. Explain the principle of drug release from implants and osmotic pump.

***

Unit ... 3

TRANSDERMAL DRUG DELIVERY SYSTEMS

♦ LEARNING OBJECTIVES ♦

After completing this chapter, student will be able to:

- ❖ Explain about the permeation through skin, factors affecting permeation and permeation enhancer.
- ❖ Understand the components of TDDS and its formulation approaches.
- ❖ Understand about the approaches for GRDDS – Floating, high density systems, inflatable and gastroadhesive systems and their applications.
- ❖ Explain the Nasal and Pulmonary routes of drug delivery and Formulation of Inhalers (dry powder and metered dose), nasal sprays, nebulizers.

3.1 INTRODUCTION

Transdermal drug delivery system (TDDS) is one of the systems lying under the category of controlled drug delivery, in which the aim is to deliver the drug through the skin in a predetermined and controlled rate. TDDS are adhesive drug-containing devices of defined surface area that deliver a predetermined amount of drug to the surface of intact skin at a programmed rate to reach the systemic circulation.

Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first-pass metabolism, respectively. Transdermal route has vied with oral treatment as the most successful innovative research area in drug delivery, as oral treatment involves attainment and maintenance of drug concentration in the body within a therapeutically effective range by introduction of a fixed dose at regular intervals, due to which the drug concentration in the body follows a peak and trough profile, leading to a greater chance of adverse effects or therapeutic failure; large amount of drug is lost in the vicinity of the target organ and close attention is required to monitor therapy to avoid overdosing. The limitations of the oral route can be overcome and benefits of intravenous drug infusion such as to bypass hepatic "first pass" hepatic elimination (HEPE) to maintain constant prolonged and therapeutic effective drug levels in the body can be closely duplicated, without its potential hazards, by transdermal drug administration through intact skin.

3.2 PERMEATION THROUGH SKIN

3.2.1 Skin: The Largest Organ

The skin is the largest organ of the human body which covers a surface area of approximately 2 sq. m. and receives about one third of the blood circulation through the body. It serves as a permeability barrier against the transdermal absorption of various chemical and biological agents. It is one of the most readily available organs of the body with a thickness of few millimeters (2.97 - 0.28 mm) which,

- Separates the underlying blood circulation network from the outside environment.
- Serves as a barrier against physical, chemical and microbiological attacks.
- Acts as a thermostat in maintaining body temperature.
- Plays role in the regulation of blood pressure.
- Protects against the penetration of UV rays.
- Skin is a major factor in determining the various drug delivery aspects like permeation and absorption of drug across the dermis. The diffusional resistance of the skin is greatly dependent on its anatomy and ultrastructure.

3.2.2 Anatomy of Skin

The structure of human skin (Fig. 3.1) can be categorized into four main layers:

- The epidermis.
- The viable epidermis.
- A non-viable epidermis (*Stratum corneum).*
- The overlying dermis.

The innermost subcutaneous fat layer (Hypodermis).

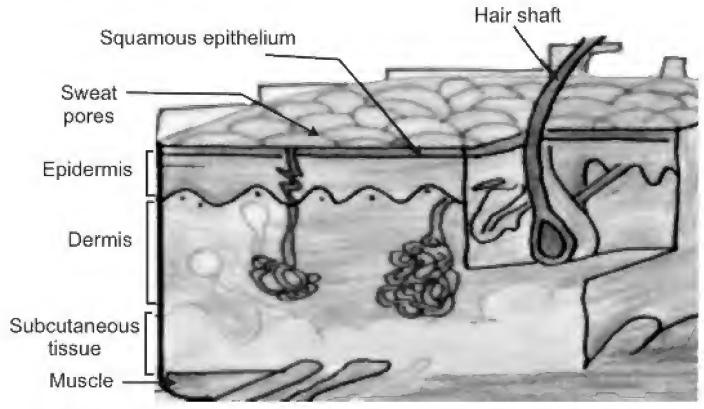


Fig. 3.1: Schematic Representation of Skin and Its Appendages

3.2.2.1 The Epidermis

The epidermis is a continually self-renewing, stratified squamous epithelium covering the entire outer surface of the body and primarily composed of two parts: the living or viable cells of the malpighian layer (viable epidermis) and the dead cells of the *stratum corneum* commonly referred to as the horny layer. Viable epidermis is further classified into four distinct layers as shown in Fig. 3.2.

- *Stratum lucidum*
- *Stratum granulosum*
- *Stratum spinosum*
- *Stratum basale*

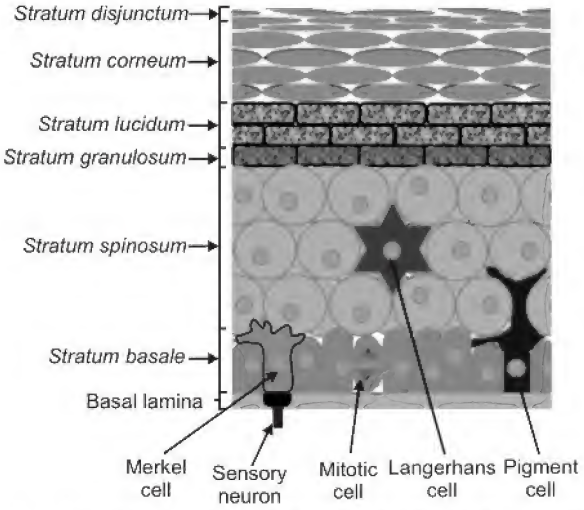


Fig. 3.2: Schematic Representation of Anatomy of Epidermis

Stratum Corneum:

This is the outermost layer of skin also called as horny layer. It is the rate limiting barrier that restricts the inward and outward movement of chemical substances. The barrier nature of the horny layer depends critically on its constituents: 75-80% proteins, 5-15% lipids, and 5-10% ondansetron material on a dry weight basis.

Stratum corneum is approximately 10 mm thick when dry, but swells to several times when fully hydrated. It is flexible but relatively impermeable. The architecture of horny layer (fig. 3.3) may be modeled as a wall-like structure with protein bricks and lipid mortar. It consists of horny skin cells (corneocytes) which are connected via desmosomes (protein-rich appendages of the cell membrane). The corneocytes are embedded in a lipid matrix which plays a significant role in determining the permeability of substance across the skin.

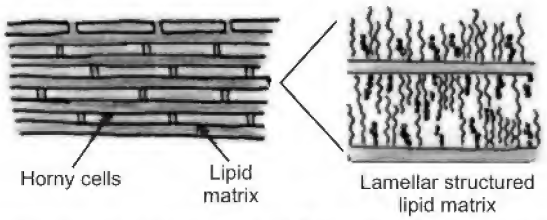


Fig. 3.3: Schematic Representation of Microstructure of Stratum Corneum

3.2.2.2 Viable Epidermis

This is situated beneath the *stratum corneum* and varies in thickness from 0.06 mm on the eyelids to 0.8 mm on the palms. Going inwards, it consists of various layers as *stratum lucidum, stratum granulosum, stratum spinosum,* and the *stratum basale*. In the *basale* layer, mitosis of the cells constantly renews the epidermis and this proliferation compensates the loss of dead horny cells from the skin surface. As the cells produced by the basale layer move outward, they itself alter morphologically and histo-chemically, undergoing keratinization to form the outermost layer of *stratum corneum* shown in Fig. 3.4.

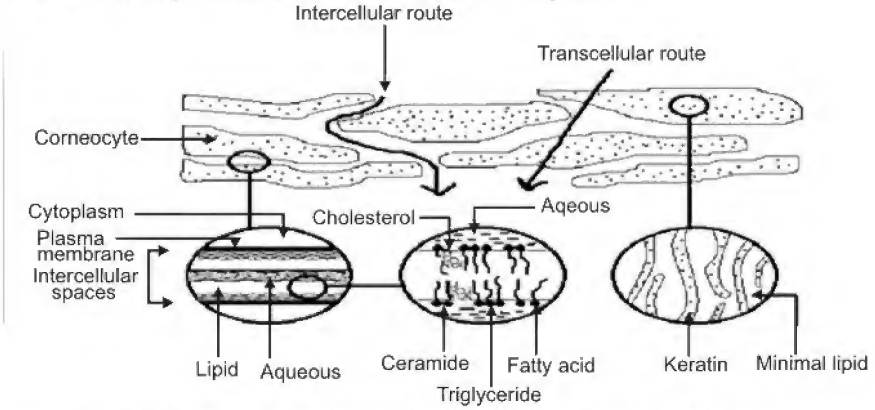


Fig. 3.4: Schematic Representation of Different Layers of Epidermis

3.2.2.3 Dermis

Dermis is the layer of skin just beneath the epidermis which is 3 to 5 mm thick layer and is composed of a matrix of connective tissues, which contains blood vessels, lymph vessels, and nerves. The cutaneous blood supply has essential function in regulation of body temperature. It also provides nutrients and oxygen to the skin, while removing toxins and waste products. Capillaries reach to within 0.2 mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus keeps the dermal concentration of permeate very low, and the resulting concentration difference across the epidermis provides the essential driving force for transdermal permeation. In terms of transdermal drug delivery, this layer is often viewed as essentially gelled water, and thus

provides a minimal barrier to the delivery of most polar drugs, although the dermal barrier may be significant when delivering highly lipophilic molecules.

3.2.2.4 Hypodermis

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It serves as a fat storage area. This layer helps to regulate temperature, provides nutritional support and mechanical protection. It carries principal blood vessels and nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, drug has to penetrate through all three layers and reach in systemic circulation.

3.2.3 Percutaneous Absorption

Before a topically applied drug can act either locally or systemically, it must penetrate through *stratum corneum*. Percutaneous absorption is defined as, "penetration of substances into various layers of skin and permeation across the skin into systemic circulation. Percutaneous absorption of drug molecules is of particular importance in transdermal drug delivery system because the drug has to be absorbed to an adequate extent and rate to achieve and maintain uniform, systemic, therapeutic levels throughout the duration of use. In general, once drug molecule crosses the stratum corneal barrier, passage into deeper dermal layers and systemic uptake occurs relatively quickly and easily.

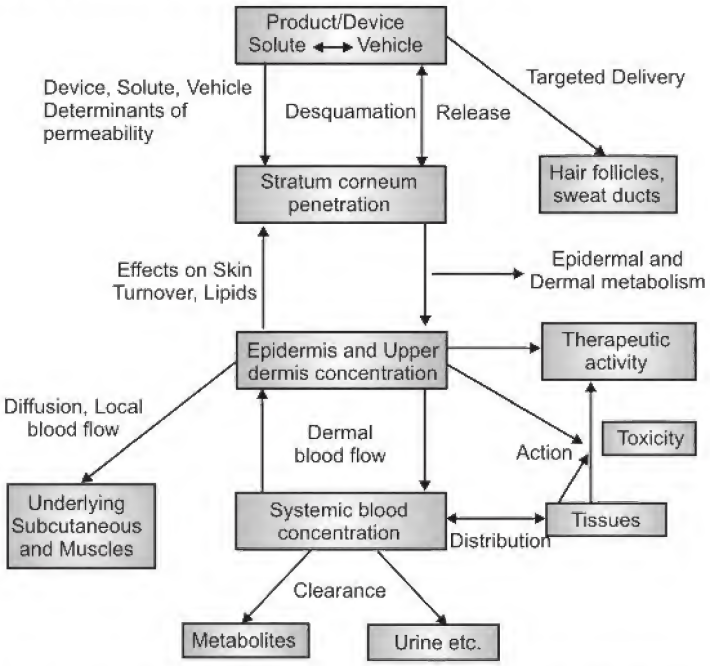


Fig. 3.5: Schematic Representation of Percutaneous Permeation

The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process (Fig. 3.5) which involves:

- Dissolution within and release from the formulation.
- Partitioning into the skin's outermost layer, the *stratum corneum* (SC).
- Diffusion through the SC, principally via a lipidic intercellular pathway.
- Partitioning from the SC into the aqueous viable epidermis, diffusion through the viable epidermis and into the upper dermis, uptake into the papillary dermis (capillary system) and into the microcirculation.

3.2.4 Routes of Drug Penetration Through Skin

In the process of percutaneous permeation, a drug molecule may pass through the epidermis itself or may get diffuse through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands as shown in Fig. 3.6. In the initial transient diffusion stage, drug molecules may penetrate the skin along the hair follicles or sweat ducts and then absorbed through the follicular epithelium and the sebaceous glands. When a steady state has been reached, the diffusion through the intact *Stratum corneum* becomes the primary pathway for transdermal permeation.

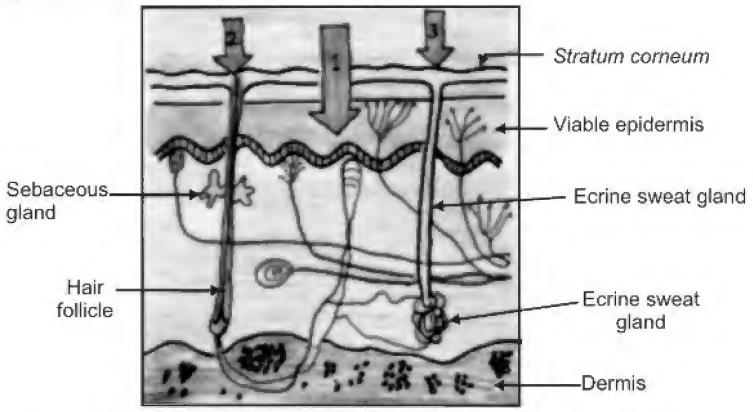


Fig. 3.6: Possible Macro Routes for Drug Penetration

For any molecules applied to the skin, two main routes of skin permeation can be defined:

- Transepidermal route
- Transfollicular route

3.2.4.1 Transepidermal Route

In transepidermal transport, molecules cross the intact horny layer. Two potential micro-routes of entry exist, the transcellular (or intracellular) and the intercellular pathway are shown in Fig. 3.7.

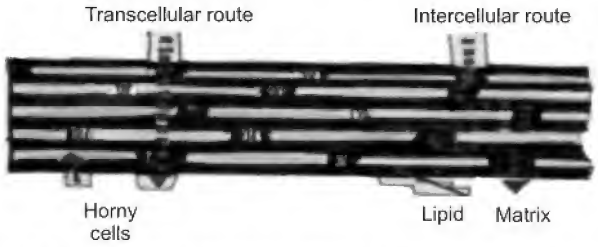


Fig. 3.7: Schematic Representation of Transepidermal Route

Both polar and non-polar substances diffuse via transcellular and intercellular routes by different mechanisms. The polar molecules mainly diffuse through the polar pathway consisting of "bound water" within the hydrated *stratum corneum* whereas, the non-polar molecules dissolve and diffuse through the non-aqueous lipid matrix of the *stratum corneum*. Thus, the principal pathway taken by a penetrant is decided mainly by the partition coefficient (log K). Hydrophilic drugs partition preferentially into the intracellular domains, whereas, lipophilic permeants (octanol/water log K > 2) traverse the *stratum corneum* via the intercellular route. Most molecules pass the *stratum corneum* by both routes.

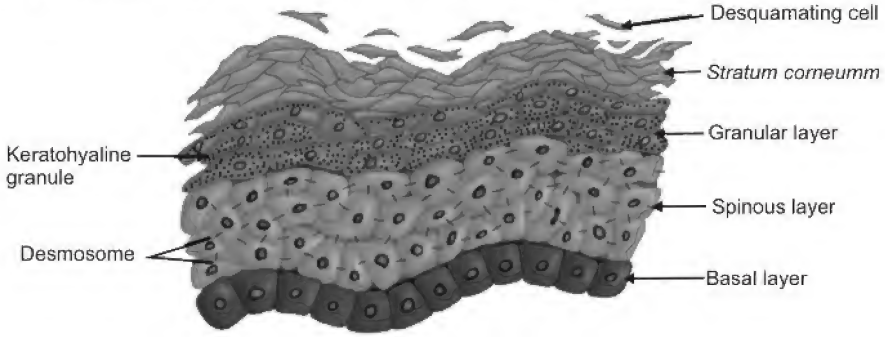


Fig. 3.8: Possible Micro Routes for Drug Penetration Across Human Skin

3.2.4.2 Intercellular or Transcellular, Transfollicular Route (Shunt Pathway)

This route comprises transport via the sweat glands and the hair follicles with their associated sebaceous glands. Although these routes offer high permeability, they are considered to be of minor importance because of their relatively small area, approximately 0.1% area of the total skin. This route seems to be most important for ions and large polar molecules which hardly permeate through the *stratum corneum*.

3.2.5 Barrier Functions of the Skin

The top layer of skin is most important function in maintaining the effectiveness of the barrier. Here the individual cells overlie each other and are tightly packed, preventing bacteria from entry and maintaining the water holding properties of the skin. Stratum

corneum mainly consists of the keratinized dead cell and water content is also less as compared to the other skin components. Lipids are secreted by the cells from the base layer of the skin to the top. These lipid molecules join up and form a tough connective network, in effect acting as the mortar between the bricks of a wall.

3.3 KINETICS OF TRANSDERMAL PERMEATION

Transdermal permeation of a drug involves the following three steps:

1. Sorption by stratum corneum.
2. Penetration of drug through viable epidermis.
3. Uptake of the drug by the capillary network in the dermal papillary layer.

The rate of permeation across the skin is given by,

$$\frac{dQ}{dt} = P_s (C_d - C_r) \quad \ldots (3.1)$$

Where, C_d and C_r are the concentrations of skin penetrate in the donor compartment and in the receptor compartment. P_s is the overall permeability coefficient of the skin tissues to the penetrate.

This permeability coefficient is given by the relationship:

$$P_s = \frac{K_{ss} D_{ss}}{h_s} \quad \ldots (3.2)$$

Where, K_s is the partition coefficient for the interfacial partitioning of the penetrate molecule from a solution medium or a transdermal therapeutic system on to the stratum corneum, D_{ss} is the apparent diffusivity for the steady state diffusion of the penetrate molecule through a thickness of skin tissues and h_s is the overall thickness of skin tissues.

As K_s, D_{ss} and h_s are constant under given conditions, the permeability coefficient (P_s) for a skin penetrate can be considered to be constant. From equation (3.1) it is clear that a constant rate of drug permeation can be obtained only when $C_d >> C^r$, i.e., the drug concentration at the surface of the stratum corneum (C_d) is consistently and substantially greater than the drug concentration in the body (C_r). Then the equation (3.1) becomes:

$$\frac{dQ}{dt} = P_s C_d \quad \ldots (3.3)$$

The rate of skin permeation (dQ/dt) is constant provided the magnitude of C_d remains fairly constant throughout the course of skin permeation. For keeping C_d constant, the drug should be released from the device at a rate (R_r) that is either constant or greater than the rate of skin uptake (R_a).

Since R_r is greater than R_a, the drug concentration on the skin surface (C_d) is maintained at a level equal to or greater than the equilibrium solubility of the drug in the *stratum*

corneum (C_s). Therefore, a maximum rate of skin permeation is obtained and is given by the equation:

$$\left(\frac{dQ}{dt}\right) m = P_s C_s$$

From the above equation, it can be seen that the maximum rate of skin permeation depends on the skin permeability coefficient (P_s) and its equilibrium solubility in the stratum corneum (C_s).

3.4 STAGES IN DRUG DELIVERY IN A TRANSDERMAL PATCH

Following are the stages in drug delivery in a transdermal patch:

1. Release of medicament from the vehicle.
2. Penetration through the skin barriers.
3. Activation of the pharmacological response.

The Transdermal patch effective therapy optimizes these steps as they are affected by three components, the drug, the vehicle and the skin. Which represents the movement of drug molecules arising from, for example, a transdermal drug delivery system with a rate-controlling membrane, illustrates the complexity of percutaneous absorption. Any drug particles must first dissolve so that molecules may diffuse towards the membrane within the patch. They penetrate partitions into the membrane, diffuse across the polymer and partitions into the skin adhesive. The molecules diffuse towards the vehicle/*stratum corneum* interface. They then partition into the *stratum corneum* and diffuse through it. Some drug may bind at a depot site; the remainder permeates further, meets a second interface, and partitions into the viable epidermis. For a lipophilic species, this partition coefficient may be unfavorable, i.e., less than 1. Within the epidermis, enzymes may metabolize the drug or it may interact at a receptor site. After passing into the dermis, additional depot regions and metabolic sites may intervene as the drug moves to capillary, partitions into its wall and out into the blood for systemic removal. A fraction of the diffusing may partition into the subcutaneous fat to form a further depot. A portion of the drug can reach deep muscle layers, as illustrated by, for example, the efficacy of non-steroidal anti-inflammatory drugs. However, there are further complications. The following factors may be important: the non-homogeneity of the tissues; the presence of lymphatics; interstitial fluid; hair follicles and sweat glands; cell division; cell transport to and through the *stratum corneum*; and cell surface loss. The disease, the healing process, the drug and vehicle components may progressively modify the skin barrier. As vehicle ingredients diffuse into the skin, cellular debris, sweat, sebum and surface contaminants pass into the dermis, changing its physicochemical characteristics. Emulsions may invert or crack when rubbed in, and volatile solvents may evaporate.

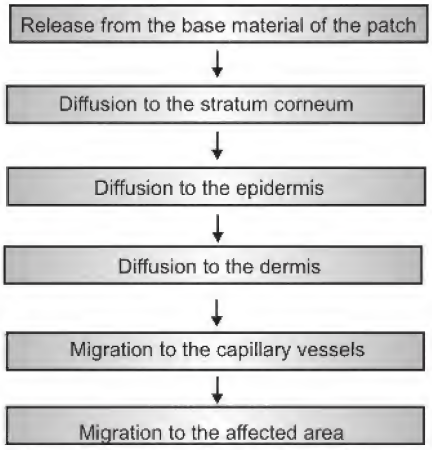


Fig. 3.9: Mechanism of Transdermal Permeation

3.5 ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM

1. Suitable for drug candidates with short half-life and low therapeutic index.
2. No first pass effect.
3. Reduction in dosing frequency.
4. Minimization of daily intake of drug.
5. Reduction of fluctuations in plasma drug concentration.
6. Improves patient compliance.
7. Minimization of side effects.
8. Simple and non-invasive.
9. Alternate route for patients who are unable to take oral medications.
10. Dose delivery unaffected by vomiting or diarrohoea.
11. Drug administration stops with patch removal.

3.6 DISADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM

1. The transdermal route of administration is unsuitable for drugs that irritate or sensitize the skin.
2. Only relatively potent drugs are suitable for transdermal delivery due to the natural limits of drug entry by the skin's impermeability.
3. Technical difficulties with the adhesion of the systems to different skin types and under various environmental conditions.
4. A constant concentration gradient is difficult to maintain.

3.7 FACTORS AFFECTING TRANSDERMAL DRUG DELIVERY SYSTEM

3.7.1 Physicochemical Properties of Drug

Following are the Physiochemical Properties of the Drug:

1. Partition coefficient
2. Molecular size
3. Solubility/Melting point
4. Ionization
5. Diffusion Coefficient

3.7.1.1 Partition Coefficient

Drug possess both water and lipid solubility. Ideal partition coefficient for intermediate transdermal delivery is log K^{1-3}. For highly lipophilic drug (log k < 3), intracellular route is favourable, whereas for hydrophilic drugs (log k < 1), it is permeated via transcellular route.

3.7.1.2 Molecular Size

Molecular size of the drug is inversely proportional to transdermal flux. The ideal molecular size of drug molecule for transdermal delivery is ≤400.

3.7.1.3 Solubility/Melting Point

Most organic solutes have high melting point and low solubility at normal temperature and pressure. Lipophilic drug permeates faster than hydrophilic substances, but it should also have aqueous solubility as needed in most of topical formulations.

3.7.1.4 Ionization

Unionized drug permeates the skin as according to pH-Partition hypothesis.

3.7.1.5 Diffusion Coefficient

Penetration of drug depends on diffusion coefficient of drug. At a constant temperature, the diffusion coefficient of drug mainly depends on properties of drug, diffusion medium and their interaction.

3.7.2 Physicochemical Properties of Drug Delivery System

Following are the Physicochemical Properties of Drug Delivery System:

1. Release characteristics.
2. Composition of drug delivery system.
3. Enhancement of Transdermal permeation.

3.7.2.1 Release Characteristics

Drug release mechanism mainly depends on drug molecules which are dissolved or suspended in the delivery system and on interfacial partition coefficient or pH of the drug from delivery system to the skin tissue. If the drug is easily released from the delivery system, the rate of transdermal permeation will be higher.

3.7.2.2 Composition of Drug Delivery System

Composition may not affect release properties but may affect its permeability functionality. For example, methyl salicylate is more lipophilic than parent acid, i.e. salicylic acid, and its percutaneous absorption is high when applied to skin in a lipoidal vehicle.

3.7.2.3 Enhancement of Transdermal Permeation

Majority of drugs will not permeate into skin for therapeutic use. Some enhancers are used for synergistic action without showing its properties (e.g. dimethyl sulphoxide, acetone, propylene glycol and tetradihydrofuryl alcohol).

3.7.3 Physiological Properties

Following are the Physiological and Pathological Conditions of Skin:

1. Skin permeation barrier in neonate and infants
2. Skin barrier properties in aged skin
3. Race
4. Skin temperature

3.7.3.1 Skin Barrier Properties in the Neonate and Young Infant

The skin surface of the newborn is slightly hydrophobic, relatively dry and rough when compared to that of older infants. Stratum corneum hydration stabilizes by the age of 3 months.

3.7.3.2 Skin Barrier Properties in Aged Skin

There are some changes in the physiology of aged skin (465 years). The moisture content of human skin decreases with age. There is a destruction of the epidermal junction and consequently, the area available for transmission into the dermis is diminished.

3.7.3.3 Race

Racial differences between black and white skins have shown some anatomical and physiological functions of the skin. In black skin, there is increased intracellular permeation due to higher lipid content and higher electrical skin resistance levels when compared to whites, but this difference is not detected in stripped skin.

3.7.3.4 Skin Temperature

The human body maintains a temperature of 32°C–37°C across the skin. Hence, increase in temperature leads to increase in diffusion through the tissue.

3.8 BASIC COMPONENTS OF TDDS

- Polymer matrix/drug reservoir
- Membrane
- Drug
- Permeation enhancers
- Pressure-sensitive adhesives (PSA)
- Backing laminates
- Release liner
- Other excipients like plasticizers and solvents

3.8.1 Polymer Matrix/Drug Reservoir

Polymers are the backbone of TDDS, which control the release of the drug from the device. A polymer matrix can be prepared by dispersion of drug in a liquid or solid state synthetic polymer base. Polymers used in TDDS should have biocompatibility and chemical

compatibility with the drug and other components of the system, such as penetration enhancers and PSAs. Additionally, they should provide consistent and effective delivery of a drug throughout the product's intended shelf-life, and should be safe.

The following criteria should be preferred in selecting the polymer to be used in the transdermal system:

(i) Molecular weight, glass transition temperature and chemical functionality of the polymer should be such that the specific drug diffuses properly and gets released through it.

(ii) The polymer should be stable, non-reactive with the drug, easily manufactured and fabricated into the desired product, and should be inexpensive.

(iii) The polymer and its degradation products must be non-toxic or non-antagonistic to the host.

(iv) The mechanical properties of the polymer should not deteriorate excessively when large amounts of active ingredients are incorporated into it.

3.8.2 Membrane

A membrane may be sealed to the backing to form a pocket to enclose the drug-containing matrix or used as a single layer in the patch construction. The diffusion properties of the membrane are used to control availability of the drug and/or excipients to the skin. For example, ethylene vinyl acetate, silicone rubber, polyurethane, etc. are used as a rate-controlling membrane.

3.8.3 Drug

For successfully developing a TDDS, the drug should be chosen with great care. Transdermal patches offer many advantages to drugs that undergo extensive first-pass metabolism, drugs with narrow therapeutic window or drugs with a short half-life, which cause non-compliance due to frequent dosing.

There are some examples of drugs that are suitable for TDDS like; Nicardipine hydrochloride, Captopril, Atenolol, Metoprolol tartarate, Clonidine, Indapamide, Propranolol hydrochloride, Carvedilol, Verapamil hydrochloride and Niterdipine, etc.

3.8.4 Permeation Enhancers

One long-standing approach for improving TDD uses penetration enhancers (also called sorption promoters or accelerants), which increase the permeability of the SC so as to attain higher therapeutic levels of the drug candidate.

Penetration enhancers interact with structural components of the SC thus, modifying the barrier functions, leading to increased permeability. Three pathways are suggested for drug penetration through the skin: polar, non-polar and polar/non-polar. The enhancers act by altering one of these pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling.

The key to altering the non-polar pathway is to alter the rigidity of the lipid structure and fluidize the crystalline pathway (this substantially increases diffusion). The fatty acid enhancers increase the fluidity of the lipid portion of the SC. Some enhancers (binary vehicles) act on both polar and non-polar pathways by altering the multi laminate pathway for penetrants. The methods employed for modifying the barrier properties of the SC to enhance the drug penetration (and absorption) through the skin can be categorized as; (1) chemical and (2) physical methods of enhancement.

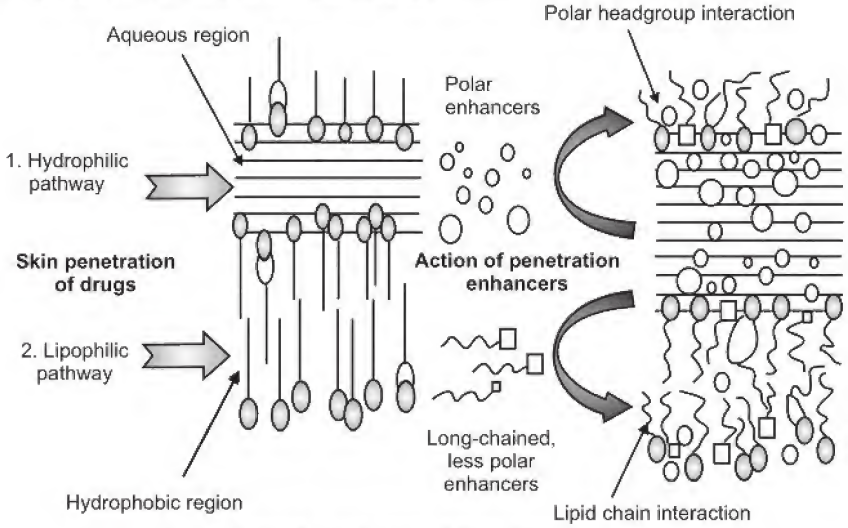


Fig. 3.10: Mode of Action of Penetration Enhancers

3.8.4.1 Chemical Enhancers

Chemicals that promote the penetration of topically applied drugs are commonly referred to as accelerants, absorption promoters or penetration enhancers.

Chemical enhancers act by:

1. Increasing (and optimizing) the thermodynamic activity of the drug when functioning as a co-solvent.
2. Increasing the partition coefficient of the drug to promote its release from the vehicle into the skin. Conditioning the SC to promote drug diffusion promoting penetration and establishing drug reservoir in the SC.
3. Some of the more desirable properties for penetration enhancers acting within the skin have been given as: They should be non-toxic, non-irritating and non-allergenic.
4. They should ideally work rapidly and the activity and duration of the effect should be both predictable and reproducible.
5. They should have no pharmacological activity within the body, i.e. should not bind to receptor sites.

6. The penetration enhancers should work unidirectionally, i.e. should allow therapeutic agents into the body while preventing the loss of endogenous material from the body.
7. When removed from the skin, barrier properties should return both rapidly and fully.
8. The penetration enhancers should be appropriate for formulation into diverse topical preparations and thus, should be compatible with both excipients and drugs.
9. They should be cosmetically acceptable with an appropriate skin "feel" some of the most widely studied permeation enhancers are sulphoxide (DMSO), fatty acids (oleic acid), alcohol (methanol), glycol (propylene glycol) and surfactant (anionic surfactant), azone (lauracapran), etc.

3.8.4.2 Physical Enhancers

Iontophoresis and ultrasound (also known as phonophoresis or sonophoresis) techniques are examples of physical means of enhancement that have been used for enhancing percutaneous penetration (and absorption) of various therapeutic agents.

3.8.5 PSAs

PSAs are the material that adhere to a substrate, in this case skin, by application of light force and leave no residue when removed. They form interatomic and intermolecular attractive forces at the interface, provided that the intimate contact is formed. To obtain this degree of contact, the material must be able to deform under slight pressure, giving rise to the term "pressure sensitive". Adhesion involves a liquid-like flow, resulting in wetting of the skin surface upon the application of pressure, and, when the pressure is removed, the adhesive sets in that state. A PSA wets and spreads onto the skin when its surface energy is less than that of the skin. After the initial adhesion, the PSA/skin bond can be built by stronger interactions (e.g., hydrogen bonding), which will depend on skin characteristics and other parameters.

Widely used PSA polymers in TDDS are polyisobutylene-based adhesives, acrylics and silicone-based PSAs, hydrocarbon resin, etc. The PSA can be located around the edge of the TDDS or be laminated as a continuous adhesive layer on the TDDS surface. The PSA should be compatible with the drug and excipients, as their presence can modify the mechanical characteristics of the PSA and the drug delivery rate.

3.8.6 Backing Laminates

Backings are chosen for appearance, flexibility and need for occlusion; hence, while designing a backing layer, the consideration of chemical resistance of the material is most important. Excipient compatibility should also be considered because the prolonged contact between the backing layer and the excipients may cause the additives to leach out of the backing layer or may lead to diffusion of excipients, drug or penetration enhancer through the layer. The most comfortable backing will be the one that exhibits lowest modulus or high flexibity, good oxygen transmission and a high moisture vapor transmission rate. Examples of backing materials are vinyl, polyethylene, polyester films, aluminum and polyolefin films.

3.8.7 Release Liner

During storage, the patch is covered by a protective liner that is removed and discarded before the application of the patch to the skin. Because the liner is in intimate contact with the TDDS, the liner should be chemically inert. Typically, a release liner is composed of a base layer that may be non-occlusive (e.g. paper fabric) or occlusive (e.g. polyethylene, polyvinyl chloride) and a release coating layer made up of silicon or teflon. Other materials used for TDDS release liner are polyester foil and metalized laminates.

3.8.8 Other Excipients Like Plasticizers and Solvents

Various solvents such as; chloroform, methanol, acetone, isopropanol and dichloromethane are used to prepare drug reservoir. In addition, plasticizers such as; dibutyl phthalate, triethyl citrate, polyethylene glycol and propylene glycol are added to provide plasticity to the transdermal patch.

3.9 VARIOUS APPROACHES TO TRANSDERMAL DEVICES

1. Membrane permeation controlled TDDS
2. Adhesive dispersion type TDDS
3. Polymer matrix diffusion controlled TDDS
4. Micro reservoir type TDDS

3.9.1 Membrane Permeation Controlled TDDS

1. In this type of TDDS, drug reservoir is sandwiched between drug impermeable backing membrane and rate controlling membrane.
2. The drug releases only through the rate controlling membrane. It can be microporous or non-porous.
3. Drug can be in the form of solution, suspension, gel or dispersion in polymer matrix in the reservoir compartment.
4. The release rate of drug from this type of system can be controlled by varying polymer composition, permeability coefficient or thickness of rate controlling membrane. On the outer surface of polymeric membrane, a thin layer of adhesive polymer is applied.
5. A constant release rate of drug.

The intrinsic rate of drug release is given by:

$$\frac{dQ}{dt} = \frac{K_{m/r} \cdot K_{a/m} \cdot D_m \cdot D_a}{K_{m/r} \cdot D_m \cdot h_a + K_{a/m} \cdot D_a \cdot h_m} C_R$$

Where, $\frac{dQ}{dt}$ = Rate of drug diffusion

C_R = Concentration of drug in reservoir

$K_{a/m}$ = Partition coefficient of drug from membrane to adhesive

$K_{m/r}$ = Partition coefficient of drug from reservoir to membrane
D_a = Diffusion coefficient in adhesive layer
D_m = Diffusion coefficient in membrane
h_a = Thickness in adhesive layer
h_m = Thickness of membrane

Fig. 3.11: Polymer Membrane Permeation Controlled TDDS

3.9.2 Adhesive Dispersion Type TDDS

1. In this type, the drug reservoir is prepared by directly dispersing the drug in an adhesive polymer.
2. Then this medicated adhesive polymer is spread over a flat sheet of drug impermeable backing membrane.
3. The drug reservoir layer is then covered by a non-medicated rate controlling polymer of constant thickness to produce an adhesive diffusion controlling DDS.
4. The rate of drug release is given as:

$$\frac{dQ}{dt} = \frac{K_{a/r} \cdot D_a}{h_a} \cdot C_R$$

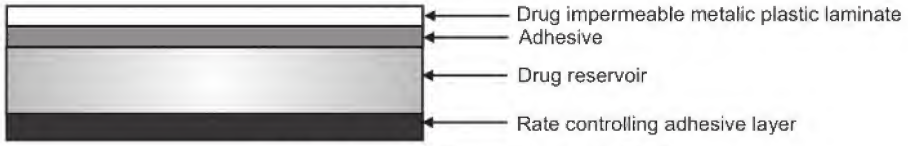


Fig. 3.12: Adhesive Dispersion Type TDDS

3.9.3 Polymer Matrix Diffusion Controlled TDDS

1. Drug reservoir is prepared by dispersing the drug homogenously in a hydrophilic and lipophilic polymer matrix.
2. The resultant medicated polymer is then moulded on a medicated disc of defined surface area and thickness.
3. The drug reservoir can also be formed by dissolving the drug and polymer in a common solvent and then evaporation of solvent at an elevated temperature.
4. This drug reservoir containing polymer disc is then pasted over a base plate containing drug impermeable backing membrane.
5. The rate of drug release is given by:

$$\frac{dQ}{dt} = \left[\frac{AC_p D_p}{2t}\right]^{1/2}$$

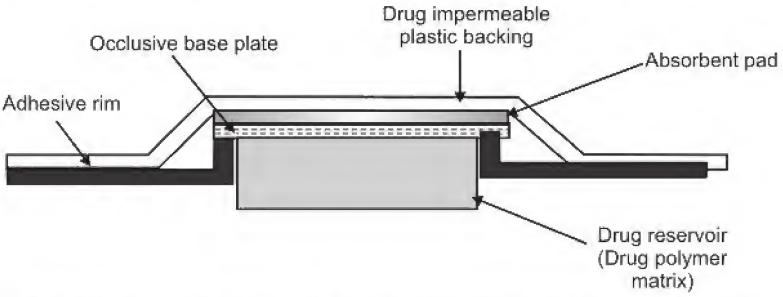


Fig. 3.13: Cross-Sectional View of Matrix Diffusion Controlled TDDS

3.9.4 Micro Reservoir Type TDDS

A combination of reservoir and matrix diffusion type drug delivery system.

1. A drug reservoir is formed by first suspending the solid drug in an aqueous solution of water soluble polymer. This drug suspension is homogenously dispersed in a lipophilic polymer by high energy dispersion technique.
2. This forms the microscopic spores of drug reservoir which are supported over an occlusive pad and are thermodynamically unstable.
3. Stabilization by cross linking the polymer chain *insitu* using cross linking agent.
4. It can be further coated with a layer of biocompatible polymer to improve the drug release.

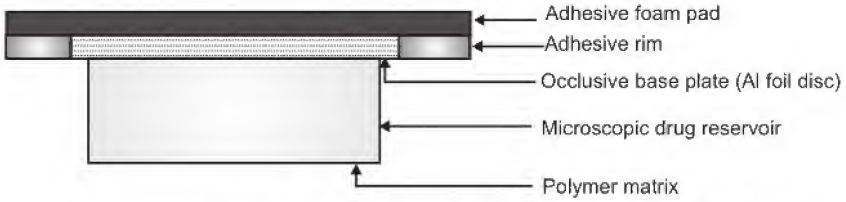


Fig. 3.14: Micro Reservoir Dissolution Controlled TDDS

GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

3.10 INTRODUCTION

Gastro-Retentive Drug Delivery System (GRDDS) has gained immense popularity in the field of oral drug delivery recently. It is a widely employed approach to retain the dosage form in the stomach for an extended period of time and release the drug slowly that can address many challenges associated with conventional oral delivery, including poor bioavailability. Different innovative approaches like magnetic field assisted gastro-retention, plug type swelling system, muco-adhesion technique, floating system with or without effervescence are being applied to fabricate GRDDS.

Gastro-retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drugs that are less soluble in a high pH environment. Also prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc.

3.10.1 Advantages of GRDDS

1. Enhanced bio-availability.
2. Reduced frequency of dosing.
3. Targeted therapy for local ailments in the upper GIT.
4. Patient compliance.
5. Improved therapeutic efficacy.

Gastro-retentive drug delivery system (GRDDS) greatly improves pharmacotherapy of the stomach through local drug release leading to high drug concentrations at gastric mucosa (eradicating *helicobacter pylori* from the sub-mucosal tissue of the stomach), making it possible to treat stomach and duodenal ulcers, gastritis and esophagitis, reduce the risk of gastric carcinoma, controlled release antacid formulations. GRDDS can be used as carriers for drugs which are absorbed from absorption windows in stomach. For example, various antibiotics, antiviral and antifungal agents etc. (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines, etc.) are taken up only from very specific sites of the GI mucosa.

3.10.2 Disadvantages of GRDDS

There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions and slow release of such drugs in the stomach is unwanted. Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastro-retentive systems. Furthermore, other drugs such as; isosorbide dinitrate that are absorbed equally well throughout the GIT will not be suitable for incorporation into a gastric retention system.

Also, GRDD's have some limitations such as:

1. Requirement of high levels of fluids in stomach for the delivery system to float and work efficiently.

2. Requires the presence of food to delay gastric emptying.
3. Drugs, which undergo significant first pass metabolism, may not be desirable candidates for floating drug delivery system since the slow gastric emptying.
4. May lead to alter systemic bioavailability.
5. Drugs having solubility or stability problems in the highly acidic gastric environment or which are irritants to gastric mucosa cannot be formulated as GRDDS.

3.10.3 Factors Controlling Gastric Retention of Dosage Forms

(a) Density of Dosage Form:

- Dosage forms having a density lower than that of gastric fluid experience floating behaviour and hence gastric retention.
- A density of <1.0 gm/ml is required to exhibit floating property.
- However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium.

(b) Shape and Size of the Dosage Form:

- The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units.
- In most cases, the larger the dosage form the greater will be the gastric retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine.
- Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes.

(c) Food Intake and Nature of Food:

- Food intake, the nature of the food, caloric content, and frequency of feeding have a profound effect on the gastric retention of dosage forms.
- The presence or absence of food in the stomach influences the GRT of the dosage form.
- Usually, the presence of food increases the GRT of the dosage form and increases drug absorption by allowing it to stay at the absorption site for a longer time.

(d) Effect of Gender, Posture and Age:

- Generally, females have slower gastric emptying rates than male.
- The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state.
- In case of elderly persons, gastric emptying is slowed down.

3.10.4 Approaches for GRDDS

1. Floating drug delivery systems.
2. Mucoadhesive systems.
3. Swellable systems.
4. High density systems.

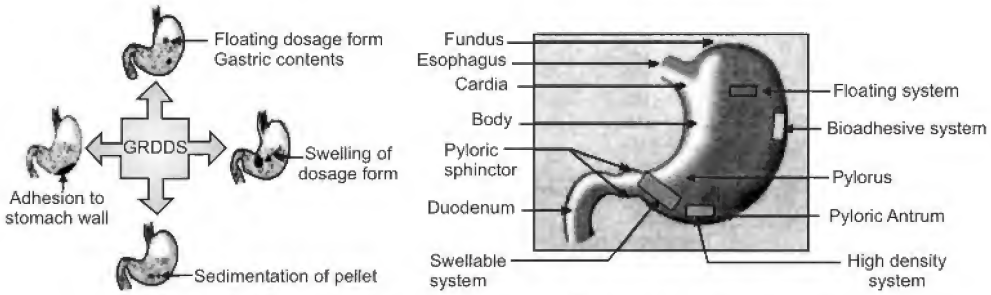


Fig. 3.15: Types of Gastro Retentive Drug Delivery System

These are explained in the articles given below.

3.10.5 Floating Drug Delivery System

Floating drug delivery systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. Floating systems can be classified into two distinct categories, (i) Non-effervescent and (ii) Effervescent systems.

Effervescent:

(a) Gas generating systems.
(b) Volatile liquid containing systems.
(c) Inflatable gastrointestinal delivery systems.
(d) Intragastric osmotically controlled drug delivery system.

Non-Effervescent:

(a) Colloidal gel barrier systems.
(b) Alginate beads.
(c) Hollow microspheres.
(d) Microporous compartment system.

3.10.5.1 Effervescent

(a) Gas Generating Systems:

Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS):

These are as shown in Fig. 3.16 and formulated by intimately mixing the CO_2 generating agents and the drug within the matrix. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release, the residual system is expelled from the stomach. This leads to an increase in the gastric retention time and a better control over fluctuations in plasma drug concentration.

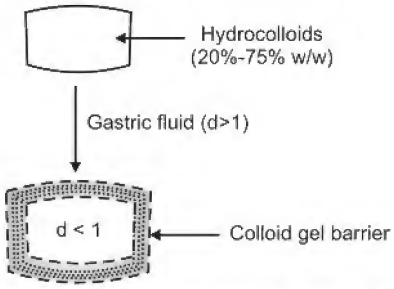


Fig. 3.16: Intra Gastric Single Layer Floating Tablets

Intra Gastric Bilayer Floating Tablets:

These are also compressed tablets as shown in Fig. 3.17 and containing two layers i.e.

(i) Immediate release layer

(ii) Sustained release layer

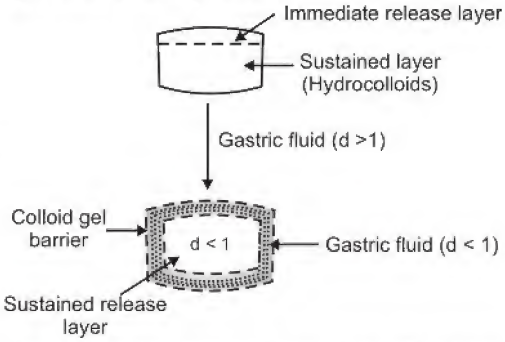


Fig. 3.17: Intra Gastric Bilayer Floating Tablets

(b) Volatile Liquid / Vacuum Containing Systems:

Intragastric Floating Gastrointestinal Drug Delivery System:

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment.

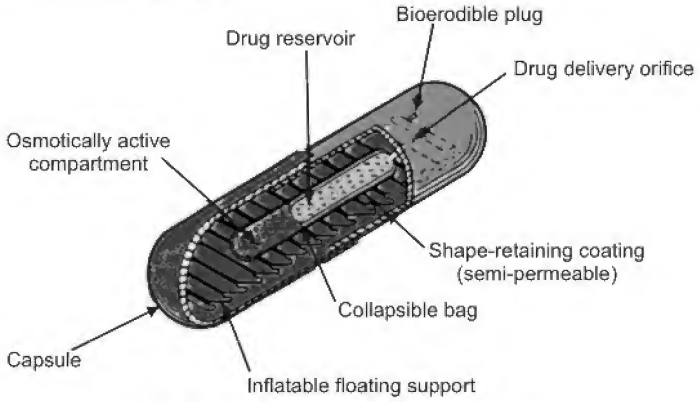


Fig. 3.18: Vacuum Containing System

(c) Inflatable Gastrointestinal Delivery Systems:

In these systems, an inflatable chamber is incorporated, which contains liquid ether that evaporates at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid.

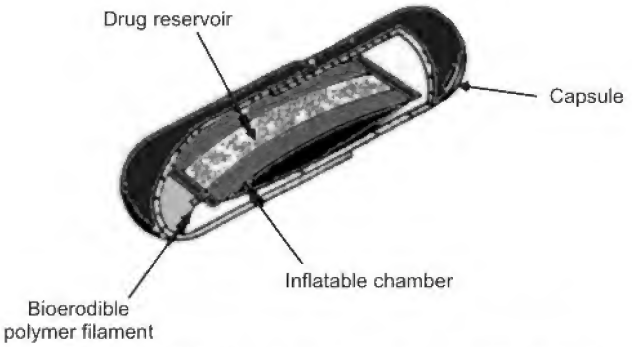


Fig. 3.19: Inflatable Gastrointestinal Delivery System

(d) Intragastric Osmotically Controlled Drug Delivery System:

It is comprised of an osmotic pressure-controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that vaporizes at body temperature to inflate the bag. The osmotic pressure-controlled drug delivery device consists of two components drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi-permeable housing. In the stomach, the water in the gastro-intestinal fluid is continuously absorbed through the semi-permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag which forces the drug reservoir compartment to reduce its volume and which in turn activate the drug release from the drug solution compartment through delivery orifice. The floating support is also made to contain a bio-erodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

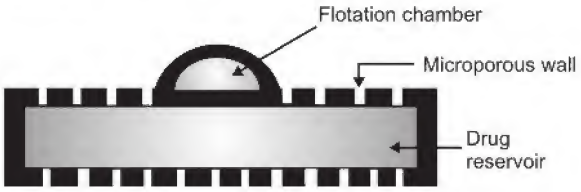


Fig. 3.20: Intragastric Osmotically Controlled Drug Delivery System

3.10.5.2 Non-Effervescent

(a) Colloidal Gel Barrier Systems:

- Such systems contain drug with gel forming hydrocolloids meant to remain buoyant on stomach contents.
- These systems incorporate a high level of one or more gel forming highly s wellable cellulose type hydrocolloids. For e.g. HPMC, NaCMC.
- On coming in contact with gastric fluids forms a viscous core.
- Incorporates H_2O and entraps air.
- Density of system falls below 1 gm/cm^3. Then it starts floating.

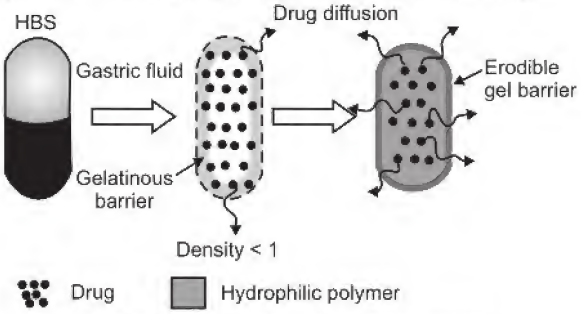


Fig. 3.21: Colloidal Gel Barrier System

(b) Microporous Membrane System:

Based on the encapsulation of drug reservoir inside a Microporous compartment,

- The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug.
- In stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents.
- Gastric fluid enters through the apertures, dissolves the drug and carries the dissolved drug for absorption.

(c) Alginate Beads:

- Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution into aqueous solutions of calcium chloride, causing precipitation of calcium alginate.

- Sodium alginate + Calcium chloride, Calcium alginate + NaCl.
- The beads are then separated and frozen in liquid nitrogen, and freeze dried at −40°C for 24 hours, leading to the formation of porous system.
- Maintain a floating force of over 12 hours.

(d) Hollow Microspheres:

- Microballoons / hollow microspheres loaded with drugs are prepared by simple solvent evaporation method.
- Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and pectin, etc.
- These systems have capacity to float on acidic dissolution media containing surfactant for about 12 hours *invitro*.

3.10.6 Bioadhesive or Mucoadhesive Drug Delivery Systems

Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bio-adhesive polymers are used and they can adhere to the epithelial surface in the stomach.

Thus, they improve the prolongation of gastric retention. The basis of adhesion is that, a dosage form can stick to the mucosal surface by different mechanisms. These mechanisms are:

1. The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.
2. The diffusion theory, which proposes physical entanglement of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.
3. The absorption theory, suggests that bio-adhesion is due to secondary forces such as; vander Waal forces and hydrogen bonding.
4. The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin network and the bio-adhesive material.

Materials commonly used for bioadhesion are poly acrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG) and polylactic acids, etc. Even though some of these polymers are effective at producing bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract (GIT).

3.10.7 Expandable, Unfoldable and Swellable Systems

A dosage form in the stomach will withstand gastric transit if it is bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations are required to develop an expandable system to prolong gastric retention time (GRT):

1. A small configuration for oral intake.
2. An expanded gastro-retentive form.
3. A final small form enabling evacuation following drug release from the device.

Thus, gastro-retentivity is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Unfoldable and swellable systems have been investigated and recently tried to develop an effective gastro-retentive drug delivery.

Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like; tetrahedron, ring or planner membrane (4 - label disc or 4 - limbed cross form) of bioerodible polymer compressed within a capsule which extends in the stomach. Swellable systems are also retained in the gastro intestinal tract (GIT) due to their mechanical properties. The swelling is usually resulting from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid. Expandable systems have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers, relatively short-lived mechanical shape memory for the unfolding system, most difficult to industrialize and not cost effective. Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion and gastropathy.

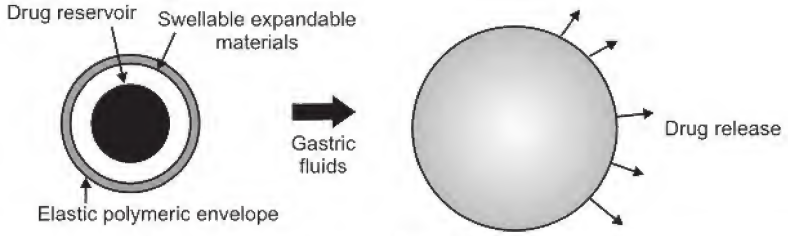


Fig. 3.22: Drug Release from Swellable System

3.11 APPLICATIONS OF GASTROADHESIVE SYSTEMS

3.11.1 Enhanced Bioavailability

- The bioavailability of riboflavin GRDF is significantly enhanced in comparison to the administration of non-GRDF polymeric formulations.
- There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

3.11.2 Sustained Drug Delivery/Reduced Frequency of Dosing

- For drugs with relatively short biological half-life, sustained and slow input from GRDF may result in improved pharmacokinetics and reduced dosing frequency.
- This feature is associated with improved patient compliance and thereby improves therapy.

3.11.3 Targeted Therapy for Local Ailments in the Upper GIT

- The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine.
- By this mode of administration, therapeutic drug concentrations may be attained locally while systemic concentrations, following drug absorption and distribution, are minimal.

3.11.4 Reduced Fluctuations of Drug Concentration

- Continuous input of the drug following GRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms.
- Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented.
- This feature is of special importance for drugs with a narrow therapeutic index.

NASAL DRUG DELIVERY SYSTEM

3.12 INTRODUCTION

Nasal drug delivery – which has been practiced for thousands of years, has been given a new lease of life. It is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as; proteins and peptides. One of the reasons for the low degree of absorption of peptides and proteins via the nasal route is rapid movement away from the absorption site in the nasal cavity due to the mucociliary clearance mechanism.

Nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption because it is permeable to more compounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus and less dilution by gastrointestinal contents. Many drugs have shown to achieve better systemic bioavailability through nasal route than by oral administration. Nasal therapy, has been recognized form of treatment in the Ayurvedic systems of Indian medicine, it is also called "NASAYA KARMA".

It has been documented that nasal administration of certain hormones and steroids have resulted in a more complete absorption. This indicates the potential value of the nasal route for administration of systemic medications as well as utilizing this route for local effects. For many years' drugs have been administered nasally for both topical and systemic action. Topical administration includes the treatment of congestion, rhinitis, sinusitis and related allergic or chronic conditions, and has resulted in a variety of different medications including corticoids, antihistamines, anti-cholinergic and vasoconstrictors.

3.13 ANATOMY AND PHYSIOLOGY OF NASAL CAVITY

The nasal cavity is divided into two halves by the nasal septum and extends posterior to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril. The nasal cavity consists three main regions, i.e. nasal vestibule, olfactory region and respiratory region. The surface area in the nose can be enlarged about 150 cm by the lateral walls of the nasal cavity which includes a folded structure, it is a very high surface area compared to its small volume. This folded structure consists of three turbinates: the superior, the median and the inferior. The main nasal airway have the narrow passages, usually 1-3 mm wide, and these narrow structures are useful to nose to carry out its main functions. The nasal cavity is covered with a mucous membrane which can be divided into two areas; non-olfactory and olfactory epithelium. The non-olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, the respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport. In this way, the mucus layer is propelled in a direction from the anterior towards the posterior part of the nasal cavity. The goblet cells are present in the mucus membrane which covers the nasal turbinate and the atrium; it secretes the mucus as mucus granules which are swelling in the nasal fluid to contribute to the mucus layer.

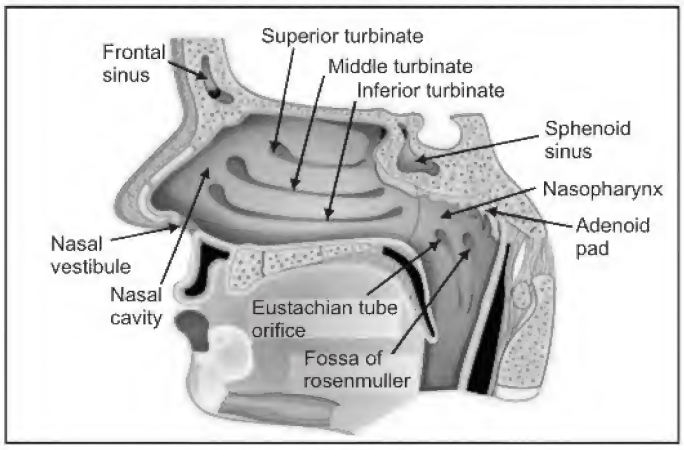


Fig. 3.23: Nasal Cavity

Normal pH of the nasal secretions in Adults: 5.5-6.5; Infants and Young Children: 5.0-6.7.

Nasal Cavity is covered with a mucous membrane. Mucus secretion is composed of 95% water, 2% Mucin, 1% Salts, 1% of other proteins such as Albumin, Lysozyme and Lactoferrin and 1% Lipids.

3.14 MECHANISM OF DRUG ACTION

Paracellular (Intercellular): Slow and passive absorption of peptides and proteins associated with intercellular spaces and tight junctions.

Transcellular: Transport of lipophilic drugs passive diffusion/active transport.

Transcytotic: Particle is taken into a vesicle and transferred to the cell.

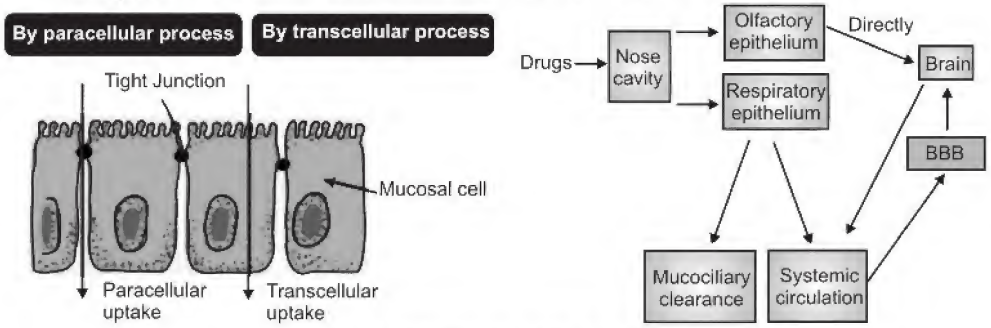


Fig. 3.24: Pathway of Drug Absorption

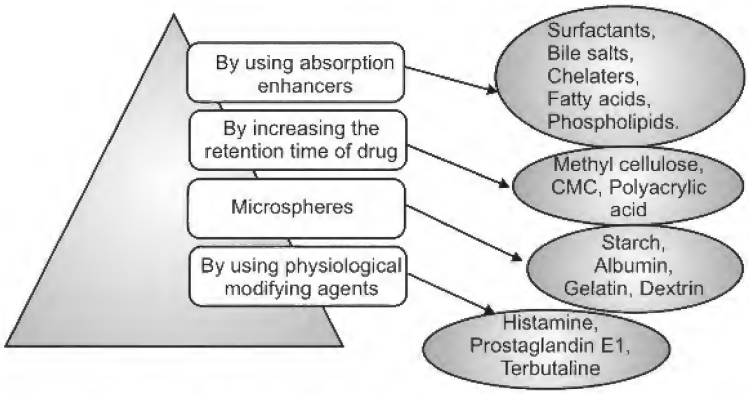


Fig. 3.25: Enhancement of Drug Absorption

3.15 ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM

1. Drug degradation that is observed in the gastrointestinal tract is absent.
2. Hepatic first pass metabolism is avoided.
3. Rapid drug absorption and quick onset of action can be achieved.
4. The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
5. The nasal bioavailability for smaller drug molecules is good.

6. Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.
7. Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
8. Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.
9. Drugs possessing poor stability in G.I.T. fluids are given by nasal route.
10. Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery.

3.16 DISADVANTAGES OF NASAL DRUG DELIVERY SYSTEM

1. The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
2. Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
3. Nasal cavity provides smaller absorption surface area when compared to GIT.
4. There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
5. Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.
6. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.

The different approaches:

1. **Prodrug Approach:** The absorption of peptides like angiotensin II, Bradykinin, Vasopressin and Calcitonin are improved when prepared into enamine derivatives.
2. **Structural Modification:** Chemical modification of Salmon Calcitonin to ecatonin (C-N bond replaces the S-S bond) showed better bioavailability.
3. **Particulate drug Delivery:**
   (i) Microspheres, Nanoparticles and Liposomes.
   (ii) Nasal Enzyme Inhibitors.
   - Peptides and Proteases.
   - Triptin Aprotinin, Borovaline, Amastatin, Betaststin and Boroleucin inhibitors.

The Components of the Nasal Formulations:

- Drug - Terbutaline sulphate.
- Viscosifying Agents - Hydroxypropyl cellulose.
- Solubilizers - Glycol, Alcohol, Cyclodextrins.

- Surfactants - SLS, Polyacrylic acid.
- Bio-adhesive Polymers - Methylcellulose, Carboxymethylcellulose.
- Preservatives - Parabens, Benzalkonium chloride.
- Antioxidants - Sodium metabisulphite.

3.17 NASAL FORMULATIONS

1. Nasal Gels: These are highly viscous, thickened solutions or suspensions. Theses have following advantages:

- Reduction of post nasal drip due to high viscosity.
- Reduction of taste impact due to reduced swallowing.
- Reduction of anterior leakage of the formulation.

These are useful as there is reduction of irritation by using emollient excipients.

2. Nasal Drops: These are one of the simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of the dose precision and therefore nasal drops may not be suitable for prescription products. It has been reported that nasal drops deposit Human Serum albumin in the nostrils more efficiently than nasal sprays.

3. Nasal Ointments: These are translucent, homogenous, viscous, semi-solid preparations intended to be instilled in the nose. Due to their viscosity they will not ooze out of the nose.

4. Nasal Sprays: Solution and Suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25-200 µm. The particle size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.

5. Nasal Powder: This dosage form may be developed if solution and suspension dosage forms cannot be developed. For e.g. due to lack of drug stability.

The advantages of the nasal powder dosage form are the absence of preservative and superior stability of the formulation. However, the suitability of powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug and/or excipients. Local application of drug is another advantage of this system.

6. Liposomes: Liposomal nasal solutions can be formulated as drug alone or in combination with pharmaceutically acceptable excipients. They are administered to the respiratory tract as an aerosol or solution for a nebulizer, or as a microfine powder for insufflations, above or in combination with an inert carrier such as; lactose, the particles of the formulation have diameters of less than 50 microns.

7. Microspheres: The main usefulness of specialized system in designed nasal products is that, it prolongs the contact with the nasal mucosa. The microspheres in their powder form

swell in contact with nasal mucosa to form a gel and controls the rate of clearance from the nasal cavity. Thus, increases the absorption and bioavailability by adhering to the nasal mucosa and increases the nasal residence time of drug. The ideal microsphere particle size requirement for nasal delivery should range from 10-50 µm as smaller particles.

3.18 APPLICATIONS OF NASAL DRUG DELIVERY SYSTEM

1. Delivery of non-peptide pharmaceuticals. For e.g. Adrenal corticosteroids, Hormones like Progesterone, Vitamin, Cardiovascular drugs, etc.
2. Delivery of peptide-based pharmaceuticals. For e.g. Insulin, Calcitonon, Pituitary hormones.
3. Delivery of diagnostic agents. For e.g. Phenolsulfonphthalein is used to diagnose kidney function.
4. Delivery of vaccines through nasal route. For e.g. Anthrax and Influenza are treated by using the nasal vaccines.
5. Delivery of drugs to brain through nasal cavity. For e.g. Parkinson's disease, Alzheimer's disease.

PULMONARY DRUG DELIVERY SYSTEM

3.19 INTRODUCTION

The respiratory tract is one of the oldest routes used for the administration of drugs. Over the past decades, inhalation therapy has established itself a valuable tool in the local therapy of pulmonary diseases such as; asthma and COPD (Chronic Obstructive Pulmonary Disease).

- This type of drug application in the therapy of these disease is a clear form of targeted drug delivery.
- The popularly marketed products are inhalation aerosol products for local pulmonary effects.
- The drug used for asthma and COPD, for e.g. β^2 agonists such as; Salbutamol (albuterol), Terbutalin formoterol, corticosteroids such as Budesonide, Flixotide or Beclomethasone and mast cell stabilizers such as Sodium cromoglycate or nedrocromi.
- The latest and probably one of the most promising applications of pulmonary drug administration is,
  1. Its use to achieve systemic absorption of the administered drug substances.
  2. Particularly for those substances that exhibit a poor bioavailability when administered by the oral route, for e.g. peptides or proteins, the respiratory tract might be convenient port of entry.

3.20 ANATOMY OF RESPIRATORY TRACT

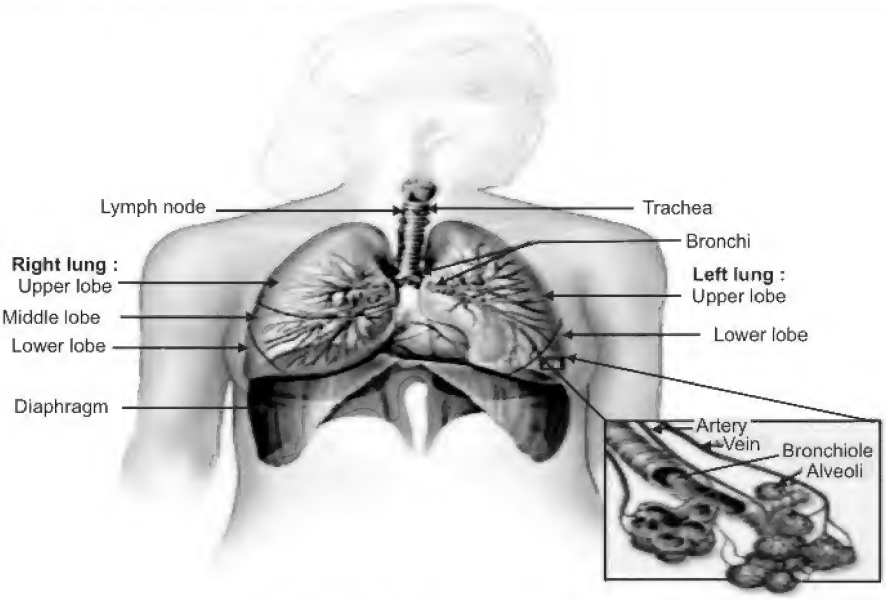


Fig. 3.26: The Respiratory Tract

The human respiratory system is a complicated organ system of very close structure-function relationships.

The system consisted of two regions:

1. The conducting system
2. The respiratory region
   - The airway is further divided into many folds: nasal cavity and the associated sinuses, and the nasopharynx, oropharynx, larynx, trachea, bronchi and bronchioles.
   - The respiratory regions consist of respiratory bronchioles, alveolar ducts and alveolar sacs.
   - The human respiratory tract is a branching system of air channels with approximately 23 bifurcations from the mouth to the alveoli. The major task of the lungs is gas exchange, by adding oxygen to and removing carbon-di-oxide from the blood passing through the pulmonary capillary bed.

3.21 ADVANTAGES OF PULMONARY DRUG DELIVERY SYSTEM

1. It is needle free pulmonary delivery.
2. It requires low and fraction of oral dose.

3. Pulmonary drug delivery having very negligible side effects since rest of body is not exposed to drug.
4. Onset of action is very quick with pulmonary drug delivery.
5. Degradation of drug by liver is avoided in pulmonary drug delivery.

3.22 DISADVANTAGES OF PULMONARY DRUG DELIVERY SYSTEM

1. Stability of drug *in-vivo.*
2. Transport.
3. Targeting specificity.
4. Drug irritation and toxicity.
5. Immunogenicity of proteins.
6. Drug retention and clearance.

The formulation approaches are as follows:

- Pulmonary delivered drugs are rapidly absorbed except large macromolecules drugs, which may yield low bioavailability due to enzymatic degradation and/or low mucosal permeability.
- Pulmonary bioavailability of drugs could be improved by including various permeation enhancers such as; surfactants, fatty acids and saccharides, chelating agents and enzyme inhibitors such as protease inhibitors.
- The most important issue is the protein stability in the formulation: the dry powder formulation may need buffers to maintain the pH, and surfactants such as; Tween to reduce any chance of protein aggregation. The stabilizers such as; sucrose are also added in the formulation to prevent denaturation during prolonged storage.
- Pulmonary bioavailability largely depends on the physical properties of the delivered protein and it is not the same for all peptide and protein drugs.
- Insulin lisomes are one of the recent approaches in the controlled release aerosol preparations. Intratracheal delivery of insulin liposomes (dipalmitoyl phosphatidylcholine : cholesterol, 7 : 2) have significantly enhanced the desired hypoglycaemic effect.
- The coating of disodium fluorescein by hydrophobic lauric acid is also an effective way to prolong the pulmonary residence time by increasing the dissolution half-life. In another method, pulmonary absorption properties were modified for protein/peptide drug (rhGCSF) in conjugation with polyethylene glycol (PEGylation) to enhance the absorption of the protein drug by using intratracheal instillation delivery in rat.

3.23 AEROSOLS

- Aerosol preparations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium. The drugs, delivered by aerosols are deposited in the airways by:
  - Gravitational sedimentation
  - Inertial impaction and
  - Diffusion
- Mostly larger drug particles are deposited by first two mechanisms in the airways, while the smaller particles get their way into the peripheral region of the lungs by following diffusion.

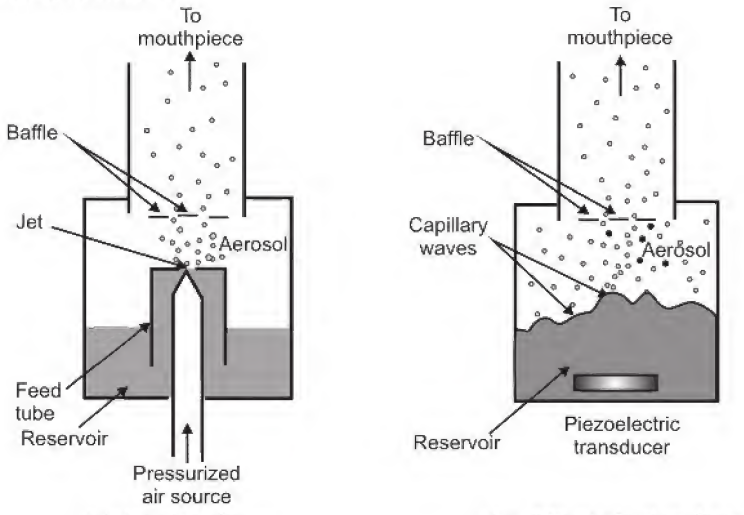
There are three commonly used clinical aerosols:

1. Jet or Ultrasonic Nebulizers
2. Metered Dose Inhalers (MDI)
3. Dry Powder Inhalers (DPI)

The basic function of these three completely different devices is to generate a drug-containing aerosol cloud that contains the highest possible fraction of particles in the desired size ranges.

Nebulizers: These are widely used as aerosolize drug solutions or suspensions for drug delivery to the respiratory tract and are predominantly useful for the treatment of hospitalized patients, delivered by the drug in the form of mist. There are two basic types:

1. Air jet
2. Ultrasonic nebulizers



(a) Jet Nebulizer **(b) Ultrasonic Nebulizer**

Fig. 3.27

3.24 METERED DOSE INHALERS (MDI)

These are used in treatment of respiratory diseases such as; asthma and COPD. They can be given in the form of suspension or solution. The particle size of less than 5 microns is observed here. This is used to minimize the number of administration errors. The main advantage is that, it can deliver measured amount of medicament accurately.

Advantages:

1. It delivers specified amount of drug.
2. Small size and convenience.
3. Usually inexpensive as compared to dry powder inhalers and nebulizers.
4. Quick to use.
5. Multidose capability more than 100 doses available.

Disadvantages:

1. Difficult to deliver high doses.
2. The remaining amount of doses is not known in MDI.
3. Accurate co-ordination between activation of a dose and inhalation is essential.

3.25 DRY POWDER INHALERS (DPI)

- DPIs are bolus drug delivery devices that contain solid drug in a dry powder mix (DPI) that is fluidized when the patient inhales.
- DPIs are typically formulated as one-phase, solid particles blends. The drug with particle sizes of less than 5 μm is used.
- DPIs are a widely accepted inhaled delivery dosage form, particularly in Europe, where they are currently used by approximately 40% of asthma patients.

Advantages:

1. Propellant free.
2. Less need for patient co-ordination.
3. Less formulation problems.
4. Dry powders are at a lower energy state, which reduces the rate of chemical degradation.

Disadvantages:

1. Dependency on patient's inspiratory flow rate and profile.
2. Device resistance and other design issues.
3. Greater potential problems in dose uniformity.
4. More expensive than pressurized metered dose inhalers.

Unit Dose Devices: Single dose powder inhalers are devices in which a powder containing capsule is placed in a holder. The capsule is opened within the device and the powder is inhaled.

Multi Dose Devises: This device is truly a metered dose powder delivery system. The drug is contained within a storage reservoir and can be dispensed into the dosing chamber by a simple back and forth twisting action on the base of the unit.

Recent Advances in Pulmonary Drug Delivery:

1. The Aerogen Pulmonary Delivery Technology.
2. The AERx Pulmonary Drug Delivery System.
3. The Spiros Inhaler Technology.
4. The Direct Haler^{TM} Pulmonary Device Platform.
5. Newer Development-Dose Counter Inhalers (DCI).

QUESTIONS

1. Define TDDS. List out the advantages and limitations of the TDDS.
2. Explain the different factors affecting percutaneous permeation of drug.
3. Explain the various types of penetration enhancers used in TDDS to enhance percutaneous absorption.
4. Describe the basic components of TDDS.
5. Enlist the different transdermal devices and explain about polymer membrane moderated device.
6. Explain about matrix dispersion type of transdermal device.
7. Define gastro retentive drug delivery system (GRDDS). Explain the purposes and benefits of gastro-retentive drug delivery.
8. Explain the various factors that control the gastro retention of dosage forms.
9. Explain briefly on the principle and design of floating type of gastro retentive DDS.
10. Describe the design of expandable gastro retentive DDS.
11. Explain the design of mucoadhesive type of gastro-retentive DDS.
12. Explain inflatable systems.
13. Write a note on Nasal Drug Delivery System.
14. Give the advantages and disadvantages of Nasal Drug Delivery System.

15. Give the Applications of Nasal Drug Delivery System.
16. Enlist and explain the components in Nasal Drug Delivery System.
17. Write a note on Pulmonary Drug Delivery System.
18. Give the advantages and disadvantages of Pulmonary Drug Delivery System.
19. Define Aerosols. Enlist and explain one type of Aerosols used in Pulmonary Drug Delivery System.
20. Write a note on Metered Dose Inhalers.
21. What are Dry Powder Inhalers (DPI's). Explain.
22. Enumerate on the Nebulizers and its types.

***

Unit ... 4

TARGETED DRUG DELIVERY SYSTEMS

♦ LEARNING OBJECTIVES ♦

After completing this chapter, student will be able to:

- ❖ Understand the basic concepts and approaches for targeted drug delivery systems.
- ❖ Explain about liposomes, niosomes, nanoparticles, monoclonal antibodies and their applications.

4.1 INTRODUCTION

Drug targeting is a special form of drug delivery system where the pharmacologically active agent or medicament is selectively targeted or delivered only to its site of action or absorption, but not to the non-target organs or tissues or cells.

The drug may be delivered:

- To the capillary bed of the active site.
- To a specific type of cell (or) even an intracellular region. Example: Tumor cell but not to normal cell.
- To a specific organ or tissue by complexing with a carrier that recognizes the target.

4.2 REASONS FOR DRUG TARGETING

The present conventional drug delivery systems have side effects and complications due to their wide distribution through the body fluids. In the treatment or prevention of diseases, the other modes of drug delivery system show non-speficity, non-selectivity and many drugs are not able to arrive at the target site in the body. Some drugs may get inactivated due to first pass metabolism or other mechanism. The localization of the drug action in injured tissues may solve this problem. To achieve a desired pharmacological response at a selected site without undesirable action with minimum side effects and better therapeutic index. For e.g. Cancer chemotherapy and enzyme replacement therapy.

4.3 IDEAL CHARACTERISTICS

Targeted drug delivery system:

- Should be biochemically inert (non-toxic) non-immunogenic.
- Should be both physically and chemically stable *in vivo* and *in vitro*.

- Should restrict drug distribution to target cells or tissues or organs.
- Should have uniform plasma distribution.
- Should be controllable and have predictable rate of drug release.
- Drug release does not affect drug action.
- Therapeutic amount of drug release.
- Minimal amount of drug release.
- Carriers used must be biodegradable or readily eliminated from the body without problem and no carrier induced modulation and diseased state.
- Preparation should be easy or reasonably simple reproductive and cost effective.

4.4 CONCEPTS AND COMPONENTS OF TDDS

Targeting of drugs to special cells and tissues of body without becoming a part of systemic circulation is a novel idea. The drug can be administered in a form such that it reaches the receptor site in sufficient concentration without disturbing an extraneous tissue cell.

Such products are prepared by considering:

- Specific properties of target cells.
- Nature of markers or transport carriers or vehicles which convey drugs to specific receptors.
- Ligands and physically modulated compounds.

1. Target cell:

Target cell could be described as a cell or group of cells in minority, identified to be in the need of treatment.

Two distinctive cellular elements present on the surface of the target cell are considered in designing the carriers for targeting via:

- Cell surface antigens- exploited in generating cell surface and non-selective antibodies.
- Cell surface and receptors which recognize and internalize the macromolecular ligands associated carriers.

Types of Targets:

- Cells, *in vitro* for genome grafting or manipulation of DNA.
- Accessible anatomical compartment i.e., peritoneal cavity cerebral vesicles, pleural cavity, lungs, lymphatics.
- Macrophages and other phagocytic cells including kuffer cells, tissue macrophages and blood macrophages or monocytes of MPS.
- Non-phagocytic cells and RES including liver endothelial cells.
- Lymphocytes and antigens present in cells.

2. Carriers:

Carrier is one of the important entities essentially required for effective transportation of the loaded drug(s). They are vectors, which sequester, retain drug and transport or deliver it

into the vicinity of target cells. Carriers can do so either through an ability inherent or acquired through structural modification to interact selectively with biological target or otherwise they are engineered to release the drug in the proximity of the target of cell line that demand optimal pharmacological action.

Types of Carriers:

(a) Physical markers for e.g. Liposomes, microspheres.
(b) Physiological markers. For e.g. Monoclonal antibodies, erythrocytes.
(c) Chemical markers such as prodrugs.

Characteristics:

- It must be able to cross anatomical barriers.
- The target cells must recognize it specifically and selectively.
- The linkage of the drug and directing unit should be stable in plasma, intestinal and other biological fluids.
- After recognition and internalization, the carrier system should release the drug moiety inside the target organs, tissues and cells.
- Carrier should be non-toxic, non-immunogenic and biodegradable.

3. Ligands:

The ligands confer recognition and speficity upon carrier/vector and lend them to approach the respective target and deliver the drug. For e.g. Antibodies, polypeptides, endogenous hormones, etc.

4.5 APPROACHES

There are mainly two approaches

(a) Chemical modification of the parent compound to a derivative which is activated only at the target site.
(b) Utilization of carriers such as; liposomes, microspheres, nanoparticles, monoclonal antibodies, cellular carriers (erythrocytes and lymphocytes), macromolecules, platelets to direct the drug at its site of action.
    (i) Prodrug approach
    (ii) Chemical delivery approach
    (iii) More approaches

- Active targeting (ligand mediated targeting).
- Passive targeting (natural targeting).
- Physical targeting.
- Chemical targeting.

(i) Prodrug Approach: A product is an active chemical derivative of a parent compound that inactivated predictably into active drug species.

(ii) Chemical Approach: It involves transformation of the active drug by synthetic means into inactive derivatives which when placed in the body will undergo several predictable enzymatic transformations principally at its site of action. This approach has proven to be successful in delivery of drugs to the eye, brain and testis.

(iii) More Approaches:

(a) Active Targeting: In active targeting, the natural disposition pattern of a carrier is modified to target specific organs, tissues or attachment of cells, specific ligand and monoclonal antibodies. It adopts modified drug carrier molecules capable of recognizing and interacting with a specific cell, tissues or organs in the body. Modification of the carrier system includes a change in molecular size, alteration of specific antibodies or attachment of cells receptor specific ligands.

(b) Passive Targeting: This refers to the natural distribution pattern of the carrier *in vivo*. Their particle size, shape, surface characteristics and the surface charge and particle numbers largely determine the disposition of the carrier. Hence it is possible to target the lungs and reticules endothermic system passives. For e.g. Different regions of GI tract, eye, nose.

(c) Physical Targeting: It refers to drugs delivery system that release a drug only when exposed to specific microenvironment such as change in pH or temperature or the use of an external magnetic field. For e.g. In the presence of certain serum protein (lipoprotein), unilamellar liposome can be designed to release their pay loads efficiently at their liquid crystalline phase temperature.

(d) Chemical Targeting: A prodrug is a pharmacologically inert form of an active drug that must undergo transformation to parent compound *in vivo* by either a chemical or enzymatic reaction to exert its therapeutic effects. Prodrugs are designated to alter the absorption, distribution and metabolism of the parent compound, thereby increase its beneficial effects and decrease its toxicity. They are also used to avoid an unpleasant taste and odour of the parent compound. For e.g. Epinephrine to eyes in the treatment of glaucoma. Acyclovir an antiviral drug in herpes infection.

4.6 ADVANTAGES OF TDDS

1. Toxicity reduced, decrease harmful system effect.
2. Drugs smaller dose gives desired effect.
3. Avoidance of first pass metabolism.
4. Increase absorption of large molecules as peptides and particulates.
5. Dose is decreased compared to conventional drug delivery.
6. No peak valley plasma concentration.
7. Selective targeting to infected cells when compared to normal cells.
8. Decrease toxicity of drugs to non-target cells.

4.7 DISADVANTAGES OF TDDS

1. Requires highly sophisticated technology for formulations.
2. Requires skill for manufacturing.
3. Drug deposition at targeted sites may produce toxic symptoms.
4. Difficult to maintain stability of the dosage form, For e.g. re-sealed RBC at 4°C.
5. Drug loading is usually low, For e.g. micelles.
6. High cost of formulation.

4.8 LIPOSOMES

4.8.1 Introduction

Liposomes are concentric bi-layered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids.

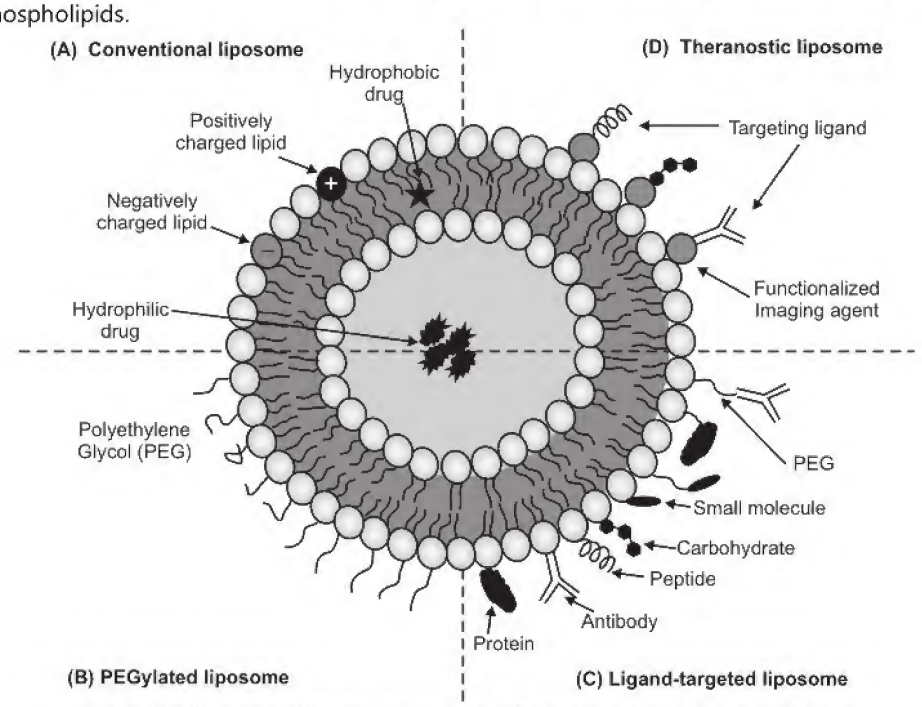
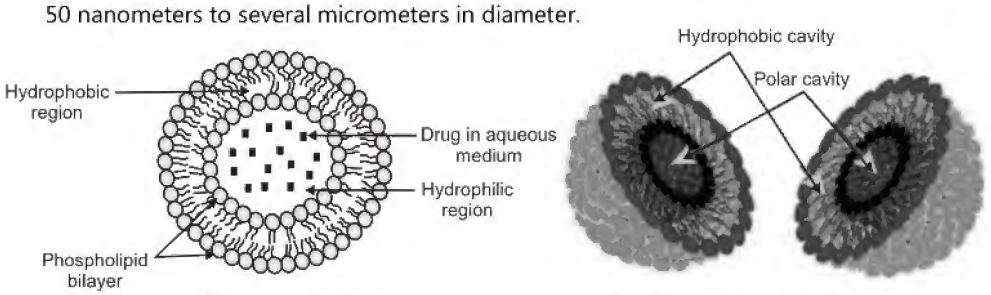


Fig. 4.1: Schematic Representation of Different Liposomal Drug Delivery

- Liposomes are microscopic spheres made from fatty materials, predominantly phospholipids.
- Liposomes are made up of one or more concentric lipid bilayers, and range in size from 50 nanometers to several micrometers in diameter.



(a) Liposome Section **(b) Liposome Cross-Section View**

Fig. 4.2

4.8.2 Structural Components of Liposomes

The main components of liposomes are:

- Phospholipids
- Cholesterol

Phospholipids:

Phospholipids are the major structural components of biological membranes. The most common phospholipid used in liposomal preparation is phosphatidylcholine (PC). Phosphatidylcholine is an amphipatic molecule containing:

- A hydrophilic polar head group, phosphocholine.
- A glycerol bridge.
- A pair of hydrophobic acyl hydrocarbon chains.

Molecules of phosphatidylcholine are not soluble in water. In aqueous media, they align themselves closely in planar bilayer sheets in order to minimize the unfavourable action between the bulk aqueous phase and the long hydrocarbon fatty chain. Then the sheets fold on themselves to form closed sealed vesicles. There are several phospholipids that can be used for the liposome preparation such as Dilaurylphosphotidylcholine (DLPC), Dimyristoylphosphotidyl choline (DMPC), Dipalmitoyl phosphotidyl choline (DPPC), Distearoylphosphotidyl choline (DSPC), Dioleolylphosphotidylcholine (DOPC), Dilaurylphosphotidyl ethanolamine (DLPE), Dimyristoylphosphotidyl ethanolamine (DMPE), Distearoylphosphotidyl ethanolamine (DSPE), Dioleoyl phosphotidyl ethanolamine (DOPE), Dilaurylphosphotidyl glycerol (DLPG), Distearoylphosphotidyl serine (DSPS).

Cholesterol:

The role of cholesterol in formulation of liposomes was given below:

1. Incorporation of sterols in liposome bilayer produces major changes in the preparation of these membranes.
2. Cholesterol itself does not form a bilayer structure.
3. However, cholesterol acts as a fluidity buffer. Cholesterol itself does not form a bilayer structure.
4. However, Cholesterol acts as a fluidity buffer. It makes the membrane less ordered and slightly more permeable below the phase transition and makes the membrane more ordered and stable above the phase transition. It can be incorporated into phospholipid membranes in very high concentration up to 1 : 1 or even 2 : 1 molar ratios of cholesterol to phospholipids.

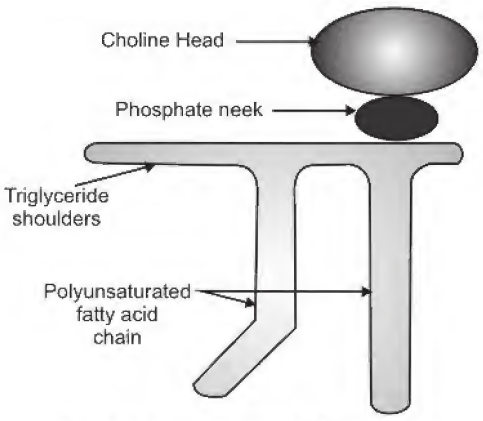


Fig. 4.3: Components of Liposome

4.8.3 Advantages of Liposomes

1. Provides selective passive targeting to tumor tissues (liposomal doxorubicin).
2. Increases efficacy and therapeutic index.
3. Increased stability via encapsulation.
4. Reduced toxicity of the encapsulated agent.
5. Site avoidance effect.
6. Improved pharmacokinetic effect (reduced elimination, increased circulating life time).
7. Flexibility to couple with site specific ligands to achieve active targeting.

4.8.4 Disadvantages of Liposomes

1. Production cost is high.
2. Leakage and fusion of encapsulated drug/molecules.
3. Sometimes phospholipids undergo oxidation and hydrolysis like reaction.
4. Short half life.
5. Low solubility.

4.8.5 Classification of Liposomes

The Liposomes may be classified based on:

1. Structure.
2. Method of preparation.
3. Composition.
4. Conventional liposome.
5. Speciality liposome.

1. Classification Based on Structures:

Table 4.1: Vesicle Type with Their Size and Number of Lipid Layers

Vesicle type	Abbreviation	Diameter size	Number of lipid layers
Unilamellar	UV	All size ranges	One
Small unilamellar	SUV	20-100 nm	One
Medium unilamellar	MUV	More than 100 nm	One
Large unilamellar	LUV	More than 100 nm	One
Giant unilamellar	GUV	More than 1.0 μm	One
Oligo lamellar	OLV	0.1-1.0 μm	Approximately 0.5
Multi lamellar	MLV	More than 0.5 μm	5-25
Multi vesicular	MV	More than 1.0 μm	Multi-compartmental structure

2. Classification Based on Method of Preparation:

Table 4.2: Different Preparation Methods and the Vesicles Formed

Preparation method	Vesicle type
Single or oligolamellar vesicle made by reverse phase evaporation	REV
Multilamellar vesicle made by reverse phase evaporation method	MLV-REV
Stable pluri lamellar vesicle	SPLV
Frozen and thawed multilamellar vesicle	FAT MLV
Vesicle prepared by extrusion technique	VET
Dehydration-Rehydration method	DRV

3. Classification Based on Composition:

Table 4.3: Different Liposomes with their Compositions

Type	Abbreviation	Composition
Conventional	CL	Neutral or negativity charge phospholipids and cholesterol.
Fusogenic	RSVE	Reconstituted sendai virus envelope.
pH sensitive	–	Phospholipids such as PER or DOPE with either CHEMS or OA.
Cationic	–	Cationic lipid with DOPE.
Long circulatory	LCL	Neutral, high temperature, cholesterol and 5-10% PEG, DSP.
Immuno	IL	CL or LCL with attached monoclonal antibody or recognition sequence.

4. Classification Based upon Conventional Liposome:

- Natural lecithin mixtures.
- Synthetic identical, chain phospholipids.
- Liposome with glycolipids.

4.8.6 Method of Preparation

I. Passive Loading Technique:

1. Mechanical Dispersion:

(a) Lipid hydration method: This is the common and most widely used method for the preparation of MLV. Round bottomed flask can be used for the preparation. The method involves formation of a thin film by drying the lipid solution and then hydrating the film by adding aqueous buffer and vertexing the dispersion. The hydration step is done at a temperature above the gel liquid crystalline transition temperature of the lipid or above the

transition temperature of the highest melting component in the lipid mixture. Depending upon their solubilities the compounds to be capsulated are added either to aqueous buffer or to organic solvent containing lipids. The disadvantages of the method include low internal volume, less encapsulation efficiency and varying size. The less encapsulation efficiency can be overcome by hydrating the lipids in presence of immiscible organic solvents like petroleum ether, diethyl ether. Then it is emulsified by sonication method. MLVs are formed by removing organic layer bypassing nitrogen.

(b) Micro emulsification: This method is used for preparing small lipid vesicles in commercial quantities. This can be achieved by micro emulsifying lipid compositions using high shearing stress generated from high pressure homogenizer. Microemulsion for biological applications can be produced by adjusting the speed of rotations from 20 to 200.

(c) Sonication: In this method, MLVs are sonicated either with a bath type sonicator or probe sonicator. The main drawbacks of this method are very low internal volume/ encapsulation efficiency, degradation of phospholipids, exclusion of large molecules, metal contamination from probe tip and presence of MLV along with SUV.

(d) French pressure cell method: The method involves the extrusion of MLV through a small orifice at 20,000 psi at 4°C. The method has several advantages over sonication method. The method is simple, rapid and reproducible and involves gentle handling of unstable materials. The resulting liposomes are larger than sonicated SUVs. The disadvantages include difficulty in achieving temperature and less working volume (about 50 ml maximum).

(e) Membrane extrusion: In this method, suspension of heterogeneous size liposomes is passed through a polymer filter having a web-like construction providing a tortuous-path capillary pore, network of interconnected, and a membrane thickness of at least about 100 microns. The processed liposomes have a narrow size distribution and selected average size less than about 0.4 microns.

(f) Dried reconstituted vesicles: In this method, the preformed liposomes are added to an aqueous solution containing drug or mixed with a lyophilized protein, followed by dehydration of mixture.

(g) Freeze-Thaw Method: In this method, the SUVs are rapidly frozen, followed by slow thawing. The sonication disperses aggregated materials to LUV. The fusion of SUV during the processes of freezing and thawing leads to the formation of ULV. This type of fusion is strongly inhibited by increasing the ionic strength of the medium and by increasing the phospholipid concentration. The entrapment efficiencies of 20 to 30% were obtained by this method.

2. Solvent Dispersion:

(a) Ethanol Injection Method: A lipid solution of ethanol is rapidly injected to an excess of buffer, which leads to the immediate formation of MLVs. The major drawback of the

method is that, the particles may be with heterogeneous size distribution (30-110 nm). Another drawback is removal of all ethanol is difficult, which may lead to form azeotrope with water.

(b) Ether Infusion Method: A solution of lipids dissolved in diethyl ether or ether methanol mixture is slowly injected to an aqueous solution of the drug, to be encapsulated at a temperature of 55°C-65°C under reduced pressure. The liposomes are reformed by subsequent removal of ether under vacuum. The main drawbacks of the method are exposure of drugs and lipids to organic solvents and high temperature which may cause degradation. Further the size may vary from 70 -190 nm.

(c) Double emulsification: In this method, a primary emulsion is prepared by dissolving the drug in an aqueous phase (w_1) which is then emulsified in an organic solvent of a polymer to make a primary w_1/o emulsion. This primary emulsion is further mixed in an emulsifier-containing aqueous solution (w_2) to make a $w_1/o/w_2$ double emulsion. The removal of the solvent leaves microspheres in the aqueous continuous phase, which are collected by filtering/centrifuging.

(d) Reverse-phase evaporation: The lipid mixture is taken in a round bottom flask followed by removal of solvent under reduced pressure by a rotary evaporator. The system is purged with nitrogen and the lipids are re-dissolved in the organic phase. The reverse phase vesicles will form in this phase. The usual solvents used are diethyl ether and isopropyl ether. Aqueous phase which contains drug to be encapsulated is added after the lipids are re-dispersed in this phase. The system is kept under continuous nitrogen and the two-phase system is sonicated until the mixture becomes clear one-phase dispersion. The mixture is then placed on the rotary evaporator and the removal of organic solvent is done until a gel is formed followed by removal of non-encapsulated material. The resulting liposomes are called reverse-phase evaporation vesicles.

3. Detergent Removal:

Lipids are solubilized by the detergents at their critical micellar concentrations. The micelles become progressively richer in phospholipid as the detergent is removed by dialysis and finally combine to form LUVs.

The advantages of detergent dialysis method are, outstanding reproducibility and production of liposome populations of homogenous size. The main drawback of the method is the retention of detergent contaminants.

II. Active Loading Technique:

(a) Proliposome: Lipid and drug are coated onto a soluble carrier to form free-flowing granular material in pro-liposome which forms an isotonic liposomal suspension on hydration. The pro-liposome approach may provide an opportunity forcost-effective large-scale manufacture of liposomes containing particularly lipophilic drugs.

(b) Lyophilization: The removal of water from products in the frozen state at extremely reduced pressure is called lyophilization (freeze drying). The process is generally used to dry products that are thermolabile which may be destroyed by heat-drying. This technique has a great potential to solve long term stability problems with respect to liposomal stability. Leakage of entrapped materials may take place during the process of freeze-drying and on reconstitution.

4.8.7 Characterization of Liposomes

The behaviour of liposomes in both physical and biological system is governed by the factors such as; physical size, membrane permeability, percent entrapped solutes, chemical composition as well as the quality and purity of the starting material.

I. Physical properties:

(a) Size and its distributions
   1. Microscopic method
   2. Laser light scattering
   3. Gel permeation

(b) Surface charge

(c) Percent capture (Entrapment)

(d) Entrapped volume

(e) Lamellarity

(f) Face behaviour of liposomes

(g) Drug release

II. Chemical properties:

(a) Quantitative determination of phospholipids.

(b) Phospholipids hydrolysis.

(c) Phospholipids oxidation.

(d) Cholesterol analysis

4.8.8 Applications of Liposomes

Liposomes may prove to be efficient carrier for targeting the drug to the site of action, because of being biodegradable innocuous nature and being identical to biological membrane.

- Liposomes are used in cancer chemotherapy and neoplasia.
- Liposomes are carriers for vaccines.
- Liposomes are used as immunological adjuvants.
- Liposomes are used as carrier of antigens.
- Liposomes are used as carrier of drug in oral treatment.

1. Arthritis e.g. Steroids – cortisol palmitate in LML liposomes.
2. Diabetics e.g. Liposomes encapsulated insulin.
   - Liposomes for topical applications e.g. steroids for skin disorder.
   - Liposomes for pulmonary delivery e.g. nebulization of drug entrapped liposomes as Benzyl Penicillin, Pentamidine, etc.
   - Leishmaniasis to treat parasitic disease with Deferrioxamine encapsulated liposomes.
   - Lysosomal storage diseases. This disease comprises a heterogenous group of syndromes. For e.g. β-Glucosidase liposomes for treatment of Gaucher's disease.
   - Cell Biological Applications. Ex-Encapsulated Polio Viruses in Liposomes
   - Metal storage disease-^{14}C labelled EDTA Phosphatidyl Ethanolamine complex into liposomes.
   - Ophthalmic delivery of drugs e.g. Idoxuridine entrapped liposomes for herpes keratitis.

4.9 NIOSOMES

Niosomes are a novel drug delivery system, which entrapped the hydrophilic drug in the core cavity and hydrophobic drugs in the non-polar region present within the bilayer hence both hydrophilic and hydrophobic drugs can be incorporated into niosomes. Niosomes are amphiphilic in nature, in which the medication is encapsulated in a vesicle which is made by non-ionic surfactant vesicles and hence the name niosomes. Their size is very small and microscopic. In the presence of proper mixtures of surfactants and charge inducing agents from the thermodynamically stable vesicles. Niosomes are mostly studied as an alternative to liposomes because they alleviate the disadvantages associated with liposomes. Niosomes overcome the disadvantages associated with liposomes such as; chemical instability. Chemical instability of liposomes is due to their predisposition to oxidative degradation and variable purity of phospholipids. The main purpose of developing niosomal system is chemical stability, biodegradability, biocompatibility, through various routes such as oral, parenteral and topical. Niosomes are used as a carrier to deliver different types of drugs such as synthetic and herbal, antigens, hormones and another bioactive compound.

Salient Features of Niosomes:

- Niosomes can entrap solutes.
- Niosomes are osmotically active and stable.
- Niosomes have an infra-structure comprising of hydrophobic and hydrophilic for the most part together, thus likewise oblige the medication atoms with an extensive variety of dissolvability.
- Niosome discharge the medication in a controlled way by means of its bilayer which give supported arrival of the encased medication, so niosomes act as medication warehouse in the body.

- Targeted medication conveyance can likewise be accomplished utilizing niosomes where the medication is conveyed especially to the body part where the remedial impact is required, thereby lessening the measurement required to be managed to accomplish the desired impact.
- They improve the solubility and oral bioavailability of poorly soluble drugs and also enhance the skin permeability of drugs when applied topically.
- Niosomes exhibits flexibility in their structural characteristics (composition, fluidity and size) and can be designed according to the desired situation.
- Niosomes can improve the performance of the drug molecules.
- Better bioavailability at the particular site, just by protecting the drug from biological environment.
- Niosomes increase the stability of the entrapped drug.
- Niosomes prolong the circulation of the entrapped drug.

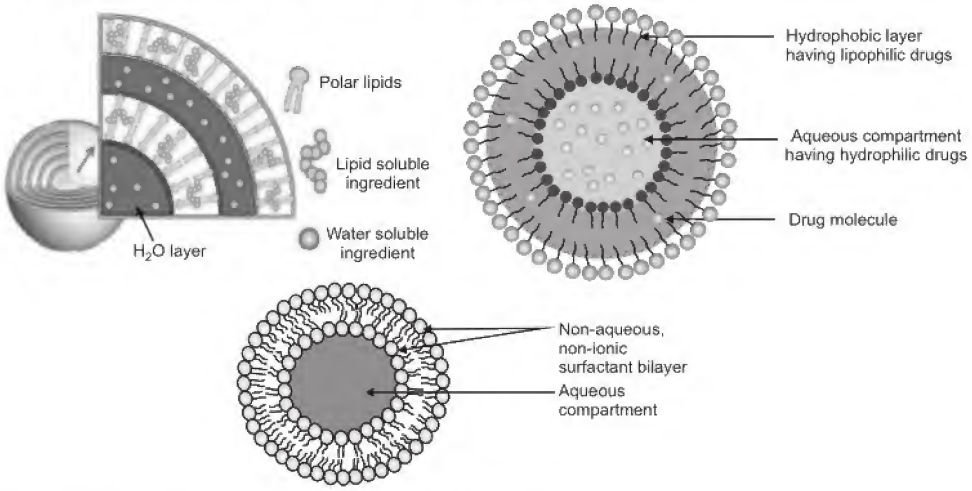


Fig. 4.4: Niosomes

4.9.1 Components of Niosomes

Niosomes mainly contains following types of components:

I. Non-ionic Surfactants: The non-ionic surfactants orient themselves in bilayer lattices where the polar or hydrophobic heads align facing aqueous bulk (media) while the hydrophobic head or hydrocarbon segments align in such a way that the interaction with the aqueous media would be minimized. To attain thermodynamic stability, every bilayer fold over itself as continuous membrane i.e. forms vesiclesso that hydrocarbon/water interface remains no more exposed.

Mainly following types of non-ionic surfactants are used for the formation of niosomes:

1. Alkyl ethers: L'Oreal described some surfactants for the preparation of niosomes containing drugs/chemicals as:

(1) Surfactant-I (molecular weight (MW 473)) is C_{16} monoalkyl glycerol ether with average of three glycerol units.

(2) Surfactant-II (MW 972) is diglycerol ether with average of the seven glycerol units.

(3) Surfactant III (MW 393) is ester linked surfactant.

Other than alkyl glycerol, alkyl glycosides and alkyl ethers, bearing polyhydroxyl head groups are also used in formulation of niosomes.

2. Alkyl esters: Sorbitan esters are most preferred surfactants used for the preparation of niosomes, amongst this category of surfactants. Vesicles prepared by the polyoxyethylene sorbitan monolaurate are relatively soluble than other surfactant vesicles. For example, polyoxyethylene (polysorbate 60) has been utilized for encapsulation of diclofenac sodium. A mixture of polyoxyethylene-10-stearylether: glyceryl laurate : cholesterol (27 : 15 : 57) has been used in transdermal delivery of cyclosporine-A.

3. Alkyl amides: Alkyl amide (e.g. galactosidesand glucosides) have been utilized to produce niosomal vesicles.

4. Fatty acid and Amino acid compounds: Long chain fatty acids and amino acid moieties have also been used in the niosome preparation.

II. Cholesterol: Steroids are important components of the cell membrane and their presence in membrane affect the bilayer fluidity and permeability. Cholesterol is a steroid derivative, which is mainly used for the formulation of niosomes. Although it may not show any role in the formation of bilayer, its importance in formation of niosomes and manipulation of layer characteristics cannot be discarded.

Cholesterol steroids are important components of:

In general, incorporation of cholesterol affects properties of niosomes like; membrane permeability, rigidity, encapsulation efficiency, ease of rehydration of freeze dried niosomes and their toxicity. It prevents the vesicle aggregation by the inclusion of molecules that stabilize the system against the formation of aggregates by repulsive steric or electrostatic forces that leads to the transition from the gel to the liquid phase in niosome systems. As a result of this, the noisome becomes less leaky in nature.

III. Charged Molecule: Some charged molecules are added to niosomes to increase stability of niosomes by electrostatic repulsion which prevents coalescence. The negatively charged molecules used are diacetyl phosphate (DCP) and phosphotidic acid. Similarly, stearylamine (STR) and stearyl pyridinium chloride are the well-known positively charged molecules used in niosomal preparations. These charged molecules are used mainly to prevent aggregation of niosomes. Only 2.5-5 mol percentage concentration of charged molecules is tolerable because high concentration can inhibit the niosome formation.

4.9.2 Methods of Preparation

Some important methods that are used to formulate niosomes are as follows:

1. Ether Injection Method: In this method, a solution containing a particular ratio of cholesterol and surfactant in ether is slowly injected into the preheated aqueous solution of the drugs maintained at 60°C through the specified gauze needle. The vaporization of ether leads to the formation of unilameller vesicles of the surfactants containing drug. Alternatively, fluorinated hydrocarbons have been used as a substitute for ether for thermolabile drugs, as they vaporize at a much lower temperature. The size of niosomes obtained by this method varies between 50-1000 mm, which mainly depend on the formulation variables and experimental conditions.

2. Hand Shaking Method: Firstly, cholesterol and surfactant are dissolved in some organic solvent (like ether, chloroform, benzene, etc.). Thereafter, solvent is evaporated under reduced pressure in a vacuum evaporator in a round bottom flask which then leaves the mixture of solid surfactant and cholesterols on the walls of round bottom flask. This layer was then rehydrated with aqueous solution containing drug with continuous shaking which results in swelling of surfactant layer. Swelled amphiphiles eventually folds and form vesicles which entrap the drugs. The liquid volume entrapped in vesicles was found to be small i.e. 5-10%.

3. Sonication Method: In this method, at first, the surfactant-cholesterol mixture is dispersed in the aqueous phase. This dispersion is then probe sonicated for 10 min at 60°C, which leads to the formation of multilamellar vesicles (MLV). These MLVs are further ultrasonicated either by probe sonicator or bath sonicator, which in turn leads to the formation of unilameller vesicles.

4. Reverse Phase Evaporation Method: In this method, the solution of cholesterol and surfactant is prepared in a mixture of ether and chloroform (1 : 1). To this, the aqueous solution of drug is added and sonicated at temperature 4°C-5°C. The solution thus obtained is further sonicated after addition of phosphate buffer saline (PBS) resulting in the formation of gel. Thereafter temperature is raised to 40°C and pressure is reduced for the removal of solvent. The PBS is added again and heated on water bath at 60°C for 10 minutes to yield niosomes.

5. Transmembrane pH Gradient (Inside Acidic) Drug Uptake Process (Remote Loading): According to this principle, the interior of niosome has the lower pH value (acidic pH) than the outer side. The added unionized basic drug crosses the niosome membrane but after entering into the niosome it gets ionized in acidic medium and is unable to leave the niosome and thus, this method increases the entrapment efficiency of such drugs. The acidic pH towards the interior of niosomes acts as an intravesicular trap for the drugs.

6. Extrusion Method: In this method, a mixture of cholesterol and diacetyl phosphate is prepared and then solvent is evaporated using rotary vacuum evaporator to leave a thin

film. The film is then hydrated with aqueous drug solution and the suspension thus obtained is extruded through the polycarbonate membrane (mean pore size 0.1 mm) and then placed in series up to eight passages to obtain uniform size niosomes.

7. Microfluidization Method: In this method, two fluidized streams (one containing drug and the other surfactant) interact at ultra-high velocity, in precisely defined microchannels within the interaction chamber in such a way that, the energy supplied to the system remains in the area of niosomes formations. This is called submerged jet principle. It results in better uniformity, smaller size and reproducibility in the formulation of niosomes.

Table 4.4: Niosomes v/s Liposomes

	Niosomes	Liposomes
Components	Surfactants	Phospholipids
Component availability	High	Low
Component purity	Good	Variable
Preparation and storage	No special conditions required.	Inert atmosphere and low temperature.
Stability	Very good.	Low.
Cost	Low.	High.

4.9.3 Applications of Niosomes

1. Better patient compliance and therapeutic effect than conventional formulations.
2. Show controlled and sustained release of drugs due to depot formation.
3. Effectively used in targeting of drugs.
4. More stable than liposome.
5. Administration through various routes like; oral, parenteral and topical, etc.
6. Biodegradable, Biocompatible and non-immunogenic to the body.
7. Handling, Storage and transportation is easy.
8. It can protect drug from enzymatic and acid thereby increasing stability of the drug.
9. It can be used in ocular drug delivery with no tissue irritation and damage by penetration enhancers.
10. To improve efficacy of drugs in cancer therapy.
11. In diagnostic imaging with carrier radio pharmaceutics.

4.10 NANOPARTICLES

4.10.1 Introduction

Nano derives from the Greek word "Nanos" which means dwarf or extremely small. It can be used as a prefix for any unit to mean a billionth of that unit. A Nanometer is a billionth of a meter or 10^{-9} m.

Nanoparticles are solid colloidal particles ranging from 1 to 1000 nm in size, they consist of macromolecular materials in which the active ingredients (drug or biologically active material) is dissolved, entrapped or encapsulated or adsorbed.

Nano capsules are the ones in which the drug is confined to an aqueous or oily core surrounded by a shell-like wall. Alternatively, the drug can be covalently attached to the surface or into the matrix.

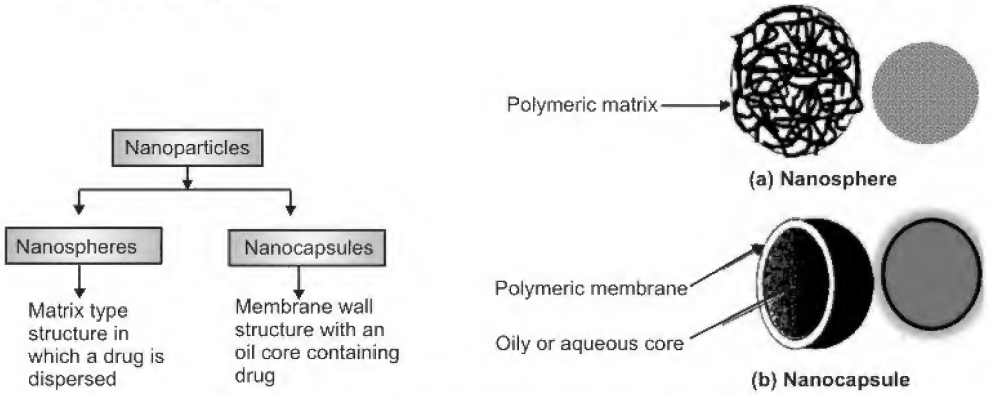


Fig. 4.5: Nanoparticles as Nanosphere and Nano Capsule

4.10.2 Advantages of Nanoparticles

1. They are suitable for different routes of administration.
2. Carrying capacity of nanoparticles is high.
3. Shelf-stability of drug increases.
4. Ability to sustain and control drug release patterns.
5. Suitable for combination therapy where two or more drugs can be co-delivered.
6. Both hydrophobic and hydrophilic drug can be incorporated.
7. System increases the bioavailability of drugs.
8. Imaging studies can be done by utilizing them.
9. It is used for targeted drug delivery of drugs.
10. Development of new medicines which are safer.

4.10.3 Disadvantages of Nanoparticles

1. The manufacturing costs of Nanoparticles are high, which result in increase in overall product cost.
2. Solvents are toxic in nature which are used in the preparation process.
3. Can start immune response and allergic reactions in body.
4. Extensive use of poly (vinyl alcohol) as stabilizer may have toxicity issues.
5. Nanoparticles are difficult to handle in physical form because particle-particle aggregation occurs due to their small size and large surface area.

4.10.4 Polymers for Nanoparticles

Polymers:

1. **Natural Hydrophilic Polymers:**
   (a) Proteins
      - Gelatin
      - Albumin
      - Lectins
      - Legumin

   (b) Polysaccharides
      - Alginates
      - Dextran
      - Chitosan
      - Agarose

2. **Semisynthetic Polymers:** Pseudolatexes or artificial latexes obtained from dispersion of preformed polymers. For e.g. Pseudolatexes of Ethylcellulose, CAP, etc.
   These are used in preparation of Nanocapsules.
3. **Synthetic Hydrophobic Polymers:**
   (a) Prepolymerized Polymers:
      - Poly (ε-caprolactone) (PECL)
      - Poly (Lactic acid) (PLA)
      - Poly (lactide co-glycolide) (PLGA)
      - Polystyrene

   (b) Polymerized in Process Polymers:
      - Poly (isobutyl cyanoacrylates) (PICA)
      - Poly (butyl cyanoacrylates) (PBCA)
      - Polyhexyl cyanoacrylates (PHCA)
      - Poly (methacrylate) (PMMA)

4.10.5 Formulation

Preparation of Nanoparticles: In the preparation of nanoparticles different types of matrix material are used, such as polysaccharides, synthetic polymer and proteins. Various factors are involved in selection of matrix material to be used in preparations which are:

(i) Required nanoparticle size.
(ii) Permeability and surface charge of nanoparticle.
(iii) Level of biodegradability and biocompatibility must be optimum.
(iv) Material must not be toxic.
(v) Solubility profile and stability of drug should not be affected.
(vi) It should show desired drug release profile.
(vii) Must not be immunogenic.

Following are methods which are used in formulation of nanoparticles:

1. Dispersion of preformed polymers.
2. Polymerization method.
3. Coacervation or ionic gelatin method.
4. Supercritical fluid technology.

1. Dispersion of Preformed Polymers:

For the preparation of biodegradable nanoparticles from polymers such as poly (lactic acid) (PLA); poly (D, L-glycolide), PLG; poly (D, L-lactide-co-glycolide) (PLGA) and Poly-(cyanoacrylate) (PCA), dispersion of preformed polymer method is used. This technique can be used in various ways as described below:

Solvent Evaporation Method:

In this method, there is conventional formation of o/w emulsion between a partially water miscible solvent containing the polymer and the drug, and an aqueous phase containing the stabilizer. In this, polymer is dissolved in an organic solvent such as; dichloromethane, chloroform or ethyl acetate. Oil in water (o/w) emulsion is prepared by emulsification of drug and polymer mixture in aqueous solution which contain emulsifying agent, which result in formation of stable emulsion. After that, by using pressure reduction method or continuous stirring, organic solvent is evaporated. The homogenizer speed, nature and stabilizer concentration along with the property of polymer effect size of nanoparticle. Usually high-speed homogenizer or ultrasonication had been used to reduce the size of nanoparticle to an optimum size.

Spontaneous Emulsification or Solvent Diffusion Method:

Also known as modified version of solvent evaporation method. In this method, two phase solvent is used, one is water miscible and other is water immiscible i.e. organic in nature which act as oil phase. In this method, interfacial turbulence is created, by immediate diffusion between two solvents (which are differing in phase), which lead to the formation of small particles. A reduction in the particle size can be gained by increasing the concentration of water miscible solvent both the above described method can be used for preparation of hydrophilic and hydrophobic drugs.

Salting Out:

It is one of commonly used method for preparation of nanoparticle. This method involves the mixing of saturated aqueous solution of polyvinyl alcohol (PVA) into an acetone solution of the polymer under magnetic stirring resulting in the formation of o/w emulsion. The precipitation of the polymer occurs when sufficient amount of water is added to external phase to allow complete diffusion of the acetone from internal phase into aqueous phase.

2. Polymerization Method:

Polymerization of monomers in an aqueous solution form the basis of this method. Two different techniques are used for the preparation in aqueous solution.

(a) **Emulsion polymerization:** This method involves emulsification of monomer in non-solvent phase.

(b) **Dispersion polymerization:** This method involves dispersion of monomer in non-solvent phase.

Incorporation of drug in nanoparticle can be achieved either by dissolving the drug in polymerization medium or by adsorption onto nanoparticle. Suspension of nanoparticles is formed, which contain surfactants and stabilizers that are used in polymerization which has to be removed by method like ultracentrifugation or by suspending them in isotonic medium which is free of surfactant. Polybutylcyanoacrylate or poly (alkylcyanoacrylate) nanoparticles are been prepared by this method. The polymer particle size had been affected by concentration of stabilizer and surfactant involved in preparation.

3. Coacervation or Ionic Gelation Method:

Chitosan, sodium alginate and gelatin are hydrophilic biodegradable polymers which are used for the preparation of nanoparticles by coacervation method. Preparation of hydrophilic chitosan nano particles by ionic gelation was developed by Calvo and Co-worker. This method involves a preparation of two aqueous phases, of which one is the polymer chitosan, adi-block co-polymer ethylene oxide or propylene oxide (PEO-PPO) and the other is a polyanion sodium tripolyphosphate which are mixed, due to mixing positively charged amino group of chitosan interacts with negative charged tripolyphosphate to form coacervates with a size in the range of nanometer. when electrostatic interaction take place between two aqueous phases coacervates are formed, and when two molecules interact due to ionic force, resulting in transition from liquid phase to gel phase at room temperature this is known as ionic gelation method.

4. Production of Nanoparticles Using Supercritical Fluid Technology:

Various conventional approaches like solvent diffusion, solvent extraction-evaporation and organic phase separation require the use of organic solvent are hazardous to the environment as well as the physiological systems. Supercritical fluid technology thus, has been invested as an alternative to prepare biodegradable micro and nanoparticles. Solvent which remain fluid in a single phase regardless of pressure above critical temperature are known as supercritical fluids. Supercritical CO_2 is the most widely used supercritical fluid. The most common processing techniques involves supercritical fluids like supercritical Antisolvent (SAS) and rapid expansion of critical solution (RESS). RESS diffuse from SAS process, in that, its solute is dissolved in super critical fluid. Thus with solvent, power of supercritical fluid decrease and the solute eventually precipitate.

Table 4.5: Polymer Used for the Preparation of Nanoparticles

Technique	Candidate drug	Polymer used
Heat denaturation and cross linking in w/o emulsion.	Hydrophilic	**Hydrophilic** Albumin, Gelatin.
Desolvation and cross linking in water.	Hydrophilic and protein affinity.	**Hydrophilic** Albumin, Gelatin.
Cross-linking in water.	Hydrophilic and protein affinity.	**Hydrophlic** Alginates and chitosan.
Polymer precipitation in an organic solvent.	Hydrophilic	**Hydrophilic** Dextran.
Emulsion polymerization.	Hydrophilic	**Hydrophobic** Poly (alkylcyanoacrylates).
Interfacial O/W polymerization	Hydrophobic	**Hydrophobic** Poly (alkylcyanoacrylates).
Solvent extraction evaporation	Hydrophilic and Hydrophobic Soluble in polar solvent.	**Polyesters** Poly (lactic acid), Poly (caprolactone).
Solvent displacement	Hydrophilic and Hydrophobic Soluble in polar solvent.	**Polyesters** Poly (lactic acid), Poly (lactide-co-glycolide).
Salting out	Soluble in polar solvent	**Polyesters** Poly (lactic acid), Poly (lactide-co-glycolide).

4.10.6 Pharmaceuticals Aspects of Nanoparticles

- It should be free from potential toxic impurities.
- It should be easy to store and administer.
- It should be sterile if parenteral use is advocated.

Process parameters performed before releasing them for clinical trials:

- Purification.
- Freeze drying.
- Sterilization.

4.10.7 Evaluation of Nanoparticles

- Nanoparticle recovery and drug incorporation efficiency.
- Size and morphology.
- Specific surface.

- Surface charge and electrophoretic mobility.
- Surface hydrophobicity.
- Density.
- Molecular weight.
- Chemical analysis.
- Protein adsorption.
- Biodegradation.
- *In vitro* drug release.

Table 4.6: Different Parameters and Characterization Methods for Nanoparticles

Parameter	Characterization method
Particle size and distribution	Photon correlation spectroscopy (PCS). Laser defractometry. Transmission electron microscopy. Scanning electron microscopy. Atomic force microscopy.
Surface hydrophobicity	Water contact angle measurement. Rose Bengal (dye) binding. X-ray photoelectron spectroscopy.
Charge determination	Laser doppler anemometry. Zeta potentiometer.
Carrier-drug interaction	Differential scanning calorimetry.
Chemical analysis of surface	Static secondary ion mass spectrometry Sorptometer.
Nanoparticle dispersion stability	Critical flocculation temperature (CFT).
Release profile	*In vitro* release characteristics under physiologic and sin conditions.
Drug stability	Bioassay of drug extracted from nanoparticles' chemical analysis of drug.

4.10.8 Applications of Nanoparticles

1. **Intracellular targeting:** They target reticuloendothelial systems for intracellular infections. For e.g. Ampicillin loaded polyhexylcyanoacrylate (PIHCA) nanoparticles for salmonellosis.
2. **Nanoparticles in chemotherapy:** It acts as a carrier for anti-tumor agents:
   - **Chemoembolization:** The approach here is, use of biodegradable particles administration to liver tumors using catheter that passes directly into an artery of the tumor.

- **Avoidance of Multidrug Resistance:** This is the main failure of the Chemotherapeutic agents. Nanoparticle loaded drugs has resulted in the effective treatment of a number of chemotherapy refractory cancers in both animals and clinical models.
- **Delivery of Anticancer Drugs:** The polyalkylcyanoacrylate Nanoparticles are possible means for targeting to specific sites in the body. The small colloidal carriers are biodegradable and drug substances can be incorporated normally by Surface adsorption. For e.g. Doxorubicinin polyalkylcyanoacrylate Nanoparticles.

3. **Nanoparticles for peroral administration of Proteins and Peptides:** The proteins and peptides are increasingly seen as therapeutic drugs, as they are susceptible to proteolytic degradation lead to stability aspect but Nanoparticle delivery help in achieving stability.
4. **Nanoparticles for intra-arterial applications:** It helps as a carrier system for the intra-arterial localization of therapeutic agents. For e.g. Dexamethasone, Heparin.
5. **Nanoparticles for ocular delivery:** It helps in improved retention of drug/wash out. For e.g. In treatment of Glaucoma therapy, with drugs like Pilocarpine.
6. **Nanoparticles for brain delivery:** The Blood-Brain Barrier represents one of the hurdles for drugs including antibiotics, antineoplastic agents and variety of neuroleptic drugs. For e.g. Brain concentration of Doxorubicin were achieved with Nanoparticles coated with Polysorbate 80.
7. **Nanoparticles for DNA Delivery Ex-Nanosphere:** DNA incubated in bovine serum was more resistant to nuclease digestion compared to bare DNA.
8. **Nanoparticles for oligonucleotide delivery ex:** A new antisense oligonucleotide (ON) carrier system based on "sponge-like" alginate nanoparticles, and they are promising carriers for specific delivery to lungs, liver and spleen.
9. **Nanoparticles for lymph targeting:** The major purpose of lymph targeting is to provide an effective anticancer chemotherapy to prevent metastatis of tumour cells by accumulating the drug in the regional lymph node via subcutaneous administration.
10. **Adjuvant in vaccines:** An adjuvant effect of the nanoparticles with either matrix entrapped or surface adsorbed vaccine has been demonstrated in several studies on subcutaneous or oral administration. For e.g. Polymethyl-methacrylate nanoparticles used as adjuvants for HIV-2 whole virus vaccine.
11. **Nanoparticles for transdermal** for application for improved absorption and permeation.
12. **Nanoparticles for enzyme** immunoassays with adsorbed enzymes.
13. **Nanoparticles for radioactive** or contrast agents for Radio-Imaging.
14. **Nanoparticles** as functionalized nanoparticles for enzyme immobilization, controlled release polymeric systems, etc.

4.11 MONOCLONAL ANTIBODIES

Monoclonal antibodies are identical immunoglobulins, generated from a single B-Cell clone. These antibodies recognize unique epitopes or binding sites on a single antigen. Derivation from a single B-Cell clones and subsequent targeting of a single epitome is what differentiates monoclonal antibodies from polyclonal antibodies.

Polyclonal antibodies are antibodies that are derived from different cell lines. They differ in amino acid sequences.

4.11.1 Characters of Monoclonal Antibodies

- Monoclonal Antibodies (mAB) are single type of antibodies that are identical and directed against a specific epitope (antigen, antigenic determinant) and are produced by B-Cell clones of a single parent or a single hybridoma cell line.
- A hybridoma cell line is formed by the fusion of one B-cell lymphocyte with a myeloma cell.
- Some myeloma cell synthesizes single mAB antibodies naturally.

4.11.2 Advantages of Monoclonal Antibodies

- Though expensive mAB are cheaper to develop than conventional drugs because it is based on tested technology.
- Side effects can be treated and reduced by using mice-human hybrid cells or by using fractions of antibodies.
- They bind to specific diseased or damaged cells needing treatment.
- They treat a wide range of conditions.

4.11.3 Disadvantages of Monoclonal Antibodies

- Time consuming method as it requires on an average of 6-9 months.
- It is very expensive and needs considerable efforts to produce them.
- Small peptide and fragment antigens may not be good antigens-monoclonal antibody may not recognize the original antigen.
- Hybridoma culture may be subject to contamination.
- System is only well developed for limited animal and not for other animals.
- More than 99% of the cells do not survive during the fusion process-reducing the range of useful antibodies that can be produced against an antigen.
- It is every possible that immunogenicity can be generated.

4.11.4 Preparation

- Monoclonal Antibodies Products or (mAB) is produced by cells lines or clones obtained from the immunized animals with the substances. Cell lines are produced by fusing B-cells from the immununized animal with myeloma cells.
- To produce the desired mAB, the cells must be grown in either of two ways:
  1. By Injection into the peritoneal cavity of a suitably prepared mouse (*in vivo* method).
  2. *In vitro* Tissue Culture.
- The vitro tissue culture is the method used when the cells are placed in culture outside the mouse, the mouse's body in flask.

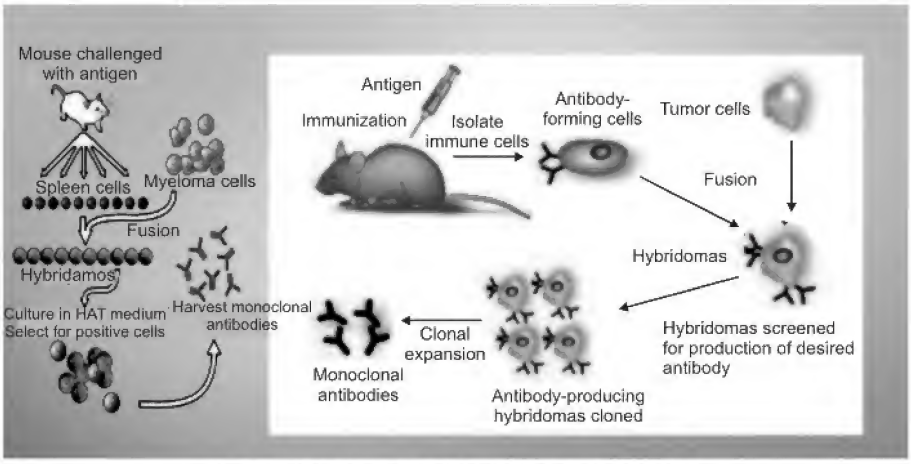


Fig. 4.6: Preparation of Monoclonal Antibodies

4.11.5 Practical Steps for Production

- Immunize animal.
- Isolate spleen cells (containing antibody - produced B-cell).
- Fuse spleen cells with myeloma cells (using PEG).
- Allow infused B-cells to die.
- Add aminopterin to culture and kill unfused myeloma cells.
- Clone remaining cells (place 1 cell/wall and allow each cell to grow into a clones of cell).
- Screen supernatant of each clone for presence of desired antibody.
- Grow chosen clone of cells in tissue culture indefinitely.
- Harvest antibody from the culture.

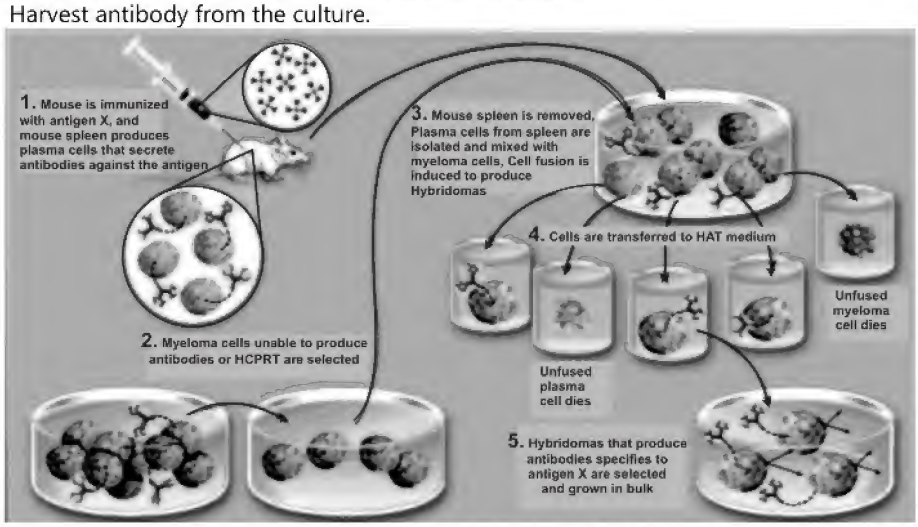


Fig. 4.7: Production of Monoclonal Antibodies

4.11.6 Applications of Monoclonal Antibodies

1. Diagnostic Applications
   (a) Biochemical analysis
   (b) Diagnostic imaging
2. Therapeutic Applications
   (a) Direct use of mAB's as therapeutic agents
   (b) mAB's as targeting agents
3. Protein Purification

1. Diagnostic Applications:

(a) Biochemical Analysis:

1. It is used in the Radioimmuno assays (RIA) and Enzyme linked Immunosorbent assays (ELISA) in the Laboratory.
2. These assays measure the circulating concentration of Hormones (Insulin, HcG-Human Chorionic Gonadotropin, Growth Hormone, Progesterone, Thyroxine, Triiodothyronine, Thyroid Stimulating Hormone) several other tissue and cell products (Blood Group antigen, Blood clotting factors, interferon's, interleukins, tumor markers).

   Example:

   (i) Pregnancy by detecting the urinary levels of HcG.
   (ii) Hormonal disorders analysis of thyroxine, triiodothyroxine.
   (iii) Cancer estimation of plasma carcinoembryonic antigen in colorectal cancers and prostate specific antigen for prostate cancer.

(b) Diagnostic Imaging:

- Radiolabelled in imaging of diseases and this technique is referred to as Immunoscintigraphy. Radioisotope commonly used for labelling mAB are Iodine-131 and technetium-99. The mAB tagged with radioisotope are injected intravenous into the patients.
- These mABs localize at specific sites (say a tumor) which can be detected by imaging the Radioactivity.
- Myocardial Infarction, DVT, Atherosclerosis, etc.

2. Direct Use of mAB's as Therapeutic Agents:

- In destroying disease-causing organisms - mAB's promote efficient opsonisation of Pathogenic organisms (by coating with antibody) and enhance Phagocytosis.
- In Immunosuppression of Organ Transplantation: In the normal medical practice, immunosuppessive drugs such as cyclosporine and prednisolone are administered to overcome the rejection of organ transplantation. Now-a-days mAB's specific to T-Lymphocyte surface antigen are being used for this purpose.

3. Protein Purification:

- mAB's can be produced for any protein so the produced mAB's purification is required against which it is raised.
- mAB's columns can be prepared by coupling them to cyanogen bromide activated sepharose (chromatographic matrix). The immobilized mAB's in this manner are very useful for the purification of Proteins by immunoaffinity method.
- There are certain advantages of using mAB's for protein purification. These include the specificity of the mAB to bid to the desired protein, very efficient elution from the chromatographic column and high degree of purification.

QUESTIONS

1. Explain the Targeted Drug Delivery System. Add a note on concepts and components of Targeted Drug Delivery System.
2. Write about the different approaches used in Targeted Drug Delivery System.
3. Give the advantages and disadvantages of Targeted Drug Delivery System.
4. Define classify Liposomes. Write about the structural components of Liposomes.
5. Give the advantages and disadvantages of Liposomes.
6. Enlist and explain any one method of preparation of Liposomes.
7. Enlist and explain the various methods for characterization of Liposomes.
8. Write about the applications of Liposomes.
9. Define Niosomes. Add a note on componenets of Niosomes.
10. Enlist and Explain any one method for preparation of Niosomes.
11. Write about the applications of Niosomes.
12. Define Nanoparticles. Give the advantages and disadvantages of Nanoparticles.

13. Write a note on Polymer used in preparation of Nanoparticles.
14. Enlist the different methods and explain any one method for preparation of Nanoparticles.
15. What are the characterization methods used in evaluation of Nanoparticles.
16. Write a note on applications of Nanoparticles.
17. What are Monoclonal Antibodies. Add a note on characters of Monoclonal Antibodies.
18. Write about the advantages and disadvantages of Monoclonal Antibodies.
19. Explain the preparation of Monoclonal Antibodies.
20. Give the applications of Monoclonal Antibodies.

***

Unit ... 5

OCULAR DRUG DELIVERY SYSTEMS

♦ LEARNING OBJECTIVES ♦

After completing this chapter, student will be able to:

- ❖ Understand the intra ocular barriers and methods to overcome.
- ❖ Explain about the Preliminary study, ocular formulations and ocuserts.
- ❖ Understand the development of intra uterine devices (IUDs) and applications.

5.1 INTRODUCTION TO EYE

The eye is a complex organ with an unique anatomy and physiology. The structure of eye can be divided into two main parts: anterior segment and posterior segment. Anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the posterior segment. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Back of the eye or posterior segment of the eye include; sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor. The anterior and posterior segment of eye is affected by various vision threatening diseases. Diseases affecting anterior segment include, but not limited to glaucoma, allergic conjunctivitis, anterior uveitis and cataract. The age-related macular degeneration (AMD) and diabetic retinopathy are the most prevalent diseases affecting posterior segment of the eye.

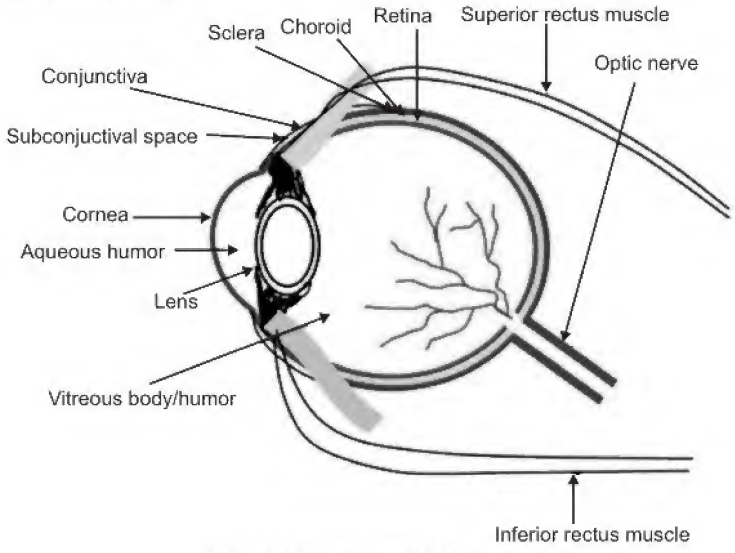


Fig. 5.1: Structure of the Eye

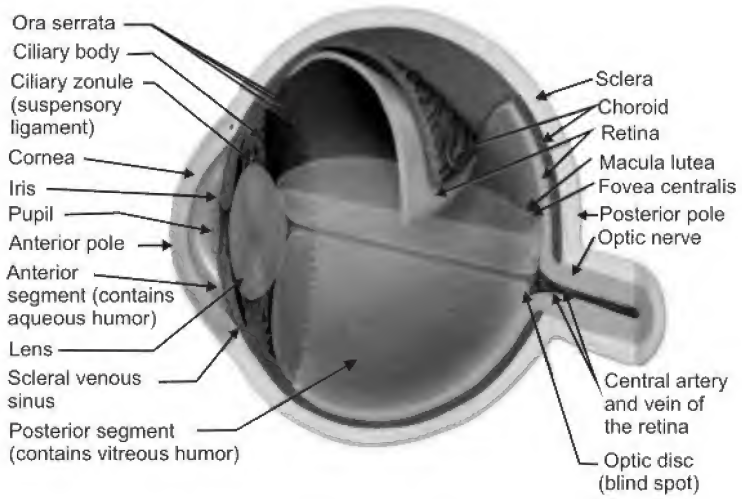


Fig. 5.2: Cross-Sectional View of Human Eye

Ocular administration of drug is primarily associated with the need to treat Ophthalmic diseases. The eye is the site for topical administration of a medication. The main objective for the ophthalmic drug delivery is that, it should sustain the drug release and to remain in the vicinity of front of the eye for prolonged period of time.

There are specialized dosage forms designed to be instilled onto the external surface of the eye (topical), administered inside (intraocular) or adjacent (periocular) to the eye or used in conjunction with an ophthalmic device.

The novel approach of drug delivery in which the drug is instilled on the cul de sac cavity of the eye (space between eye lids and eye balls) is known as Ocular Drug Delivery System.

The most commonly used employed dosage forms are the Solutions, Suspensions and Ointments. The newest dosage forms are the Gels, Gel forming Solutions, Ocular inserts, intravitreal injections and implants.

5.2 COMPOSITION OF EYE

Eye is composed of Water - 98%, Solid - 1.8%, Protein - 0.67%, Sugar - 0.65%, NaCl - 0.66%, other mineral element Sodium, Potassium and Ammonia - 0.79%.

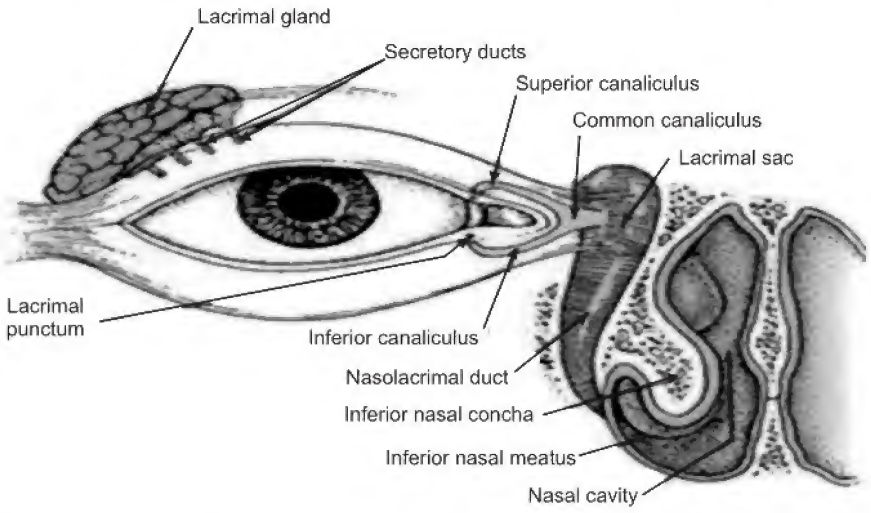


Fig. 5.3: Lacrimal Nasal Drainage

5.3 MECHANISM OF OCULAR ABSORPTION

There are two types:

1. **Non-Corneal Absorption:** The penetration is across Sclera and Conjunctiva into intra ocular tissues. It is non-productive as it restrains entry of the drug into aqueous Humour.
2. **Corneal Absorption:** The outer epithelium with rate limiting barrier, with pore size 60A and allowing only small ionic and lipophilic molecules. The trans-cellular transport is between corneal epithelium and stroma. Drugs absorbed through cornea discharge through aqueous humor into systemic routes.

5.4 FACTORS AFFECTING INTRAOCULAR BIOAVAILABILITY

1. Lacrimal fluids.
2. Naso-lacrimal drainage.
3. Interaction of drug with proteins of lacrimal fluids.
4. Dilution with tears.
5. Cornear barriers.
6. Active ion transport at cornea.

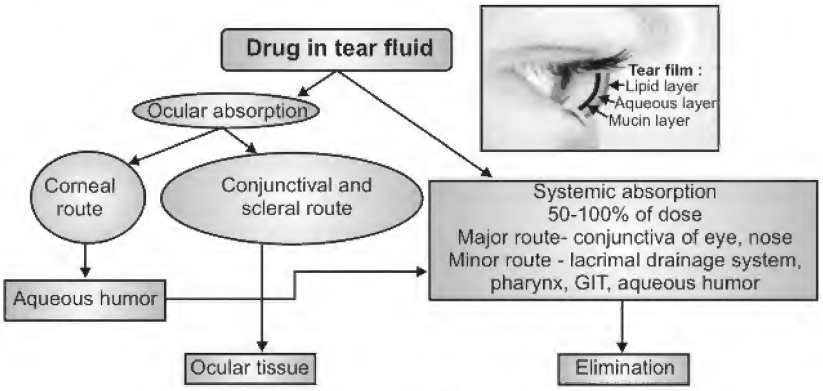


Fig. 5.4: Mechanism of Ocular Absorption

Ophthalmic dosage forms are the sterile products essentially free from foreign particles, suitably compounded and packaged for instillation in to the eye.

Some of the dosage forms have been developed to Ocular drug delivery systems.

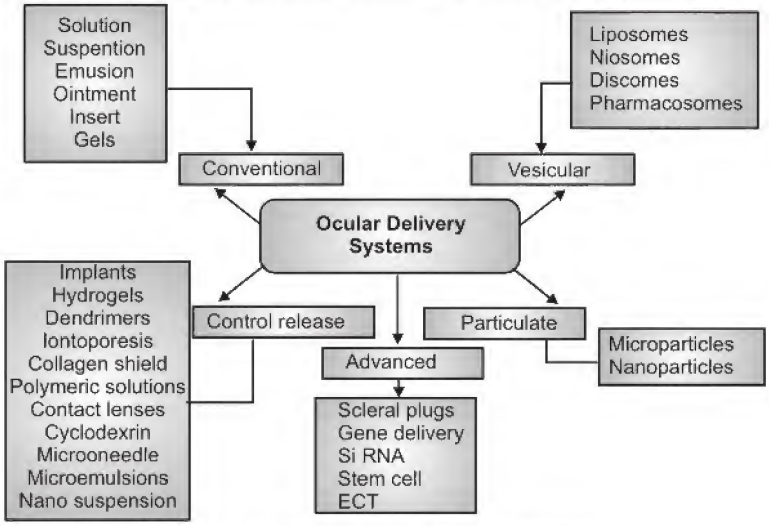


Fig. 5.5: Ocular Drug Delivery Systems

5.5 ADVANTAGES OF OCULAR DRUG DELIVERY SYSTEM

1. It can be easily administered.
2. They have quick absorption and effect.
3. Less visual and systemic side effects.
4. Better patient compliance.

5.6 DISADVANTAGES OF OCULAR DRUG DELIVERY SYSTEM

1. Residence time of drug at eye surface is less.
2. Poor bioavailability.
3. The instability of the dissolved drug.
4. The low concentration of preservative reduces shelf life after opening the bottle.

5.7 IDEAL CHARACTERISTICS OF OCULAR DRUG DELIVERY SYSTEM

1. It should be sterile.
2. It should be isotonic to body fluids.
3. Buffer/pH adjustment.
4. Less drainage tendency.
5. Minimum protein binding.

5.8 BARRIERS TO OCULAR DRUG DELIVERY

The reason why it is difficult to achieve relevant therapeutic doses within the eye is primarily due to the presence of multiple barriers. When a dosage form is either administered topically or systemically, it faces multiple obstacles before it reaches its site of action. As a result, ocular bioavailability from topically administered drug is usually only 1%-7% of the applied dose. These barriers can be broadly classified as anatomical barriers and physiological barriers.

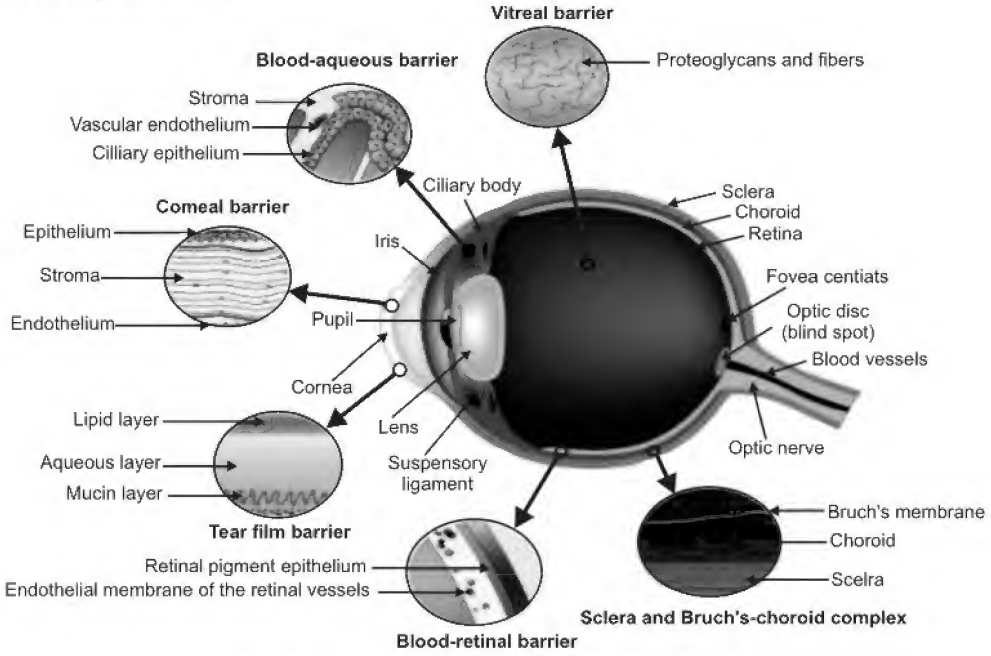


Fig. 5.6: Barriers of Ocular Drug Delivery System

1. Anatomical Barriers:

When a dosage form is topically administered, there are two routes of entry: either through the cornea or via the non-corneal route.

(a) The cornea is a very tight multilayered tissue that is mainly composed of five sections:
   (i) Epithelium-Principle barrier (Hydrophilic drug transport through intercellular spaces).
   (ii) Bowman's membrane.
   (iii) Stroma-multiple layers of collagen fibers containing pores and channels (for lipophilic drug, significant barrier).
   (iv) Descemet's membrane.
   (v) Endothelium.

Prevention: Optimum bioavailability, right balance of lipophilic and hydrophilicity.

(b) Non-corneal route bypass the cornea and involves movement across conjunctiva and sclera.

(c) Conjunctiva: It is more permeable than cornea for hydrophilic molecules.

2. Physiological Barriers:

The eye's primary line of defense is its tear film. Bioavailability of topically administered drugs is further reduced by precorneal factors such as; solution drainage, tear dilution, tear turnover, and increased lacrimation. This in turn lowers the exact time for absorption leading to reduced bioavailability.

Prevention: So, the drugs administered as eye drops need to be isotonic and non-irritating to prevent significant precorneal loss.

3. Blood Ocular Barrier:

This barrier normally keeps most drugs out of the eye, but inflammation breaks down this barrier allowing drugs and large molecules to penetrate into the eye.

(a) Blood aqueous barrier: The ciliary epithelium and capillaries of the iris.

(b) Blood retinal barrier: Non-fenestrated capillaries of the retinal circulation and tight junctions between retinal epithelial cells preventing passage of large molecules from chorio-capillaris into retina.

4. Drug and Dosage Form Related Factors:

(a) Solubility: Solubility is dependent on the pK_a of the drug and pH of the solution.

(b) Lipophilicity: Lipophilicity and corneal permeability display sigmoidal relationship. This is because of the differential permeability of the different layers of cornea towards lipophilic drugs. Lipophilic drugs tend to permeate easily through the *epithelial layers* of cornea and the hydrophilicity of the inner layer of cornea (stroma) requires higher hydrophilicity for optimal permeation.

(c) **Molecular weight and size:** The weight and size of molecules play a critical role in deciding its overall permeability through paracellular route. Molecules having molecular weight less than 500 Dalton are able to permeate readily.

(i) The conjunctiva has larger paracellular pore diameter thus allowing permeation of larger molecules such as small and medium size peptides (5000-10000 Daltons).

(ii) Permeation across sclera occurs through the aqueous pores and molecular size of the solute can be the determining factor. Sucrose (molecular weight - 342 Daltons) permeates 16 times faster than inulin (molecular weight - 5000 Daltons). Scleral permeability is approximately half of conjunctiva but much higher than cornea.

5.9 METHODS TO OVERCOME BARRIERS TO OCULAR DRUG DELIVERY

Drug delivery through topical or systemic route faces a number of challenges limiting their success. Advancements in drug design, drug formulation and devices have led to successful products. But the scientists have experimented with alternate routes of drug delivery that can overcome barriers presented by the more conventional routes. Injections through visible portions of the sclera targeting various sections of ocular structures are routinely carried out by a trained specialist.

1. Intravitreal Injections:

Intravitreal injection (IVI) involves delivering of the drug formulation directly into the vitreous humor through pars plana. This method provides direct access to the vitreous and avoids both the cornea and also the scleral blood vessels. Formulations such as; solution, suspension or a depot formulation can be administered through this route. Drug elimination occurs either through the retina or the anterior chamber through the aqueous humor following a first order rate of decline. This rate of elimination has a linear correlation with the molecular weight of the drug. Larger molecules tend to have longer half-lives as high as several weeks as compared to less than 3 days for low molecular weight compounds.

IVI administration is associated with adverse effects such as; retinal detachment, cataract, hyperemia and endophthalmitis. Sustained release drug delivery systems can help by lowering frequency of administration and thus allow for better patient compliance.

2. Subconjunctival Injections:

This injection delivers the drug beneath the conjunctival membrane that lines the inner surface of eyelid. It allows for circumvention of both cornea and conjunctiva allowing the drug direct access to the sclera. It is much less invasive with lesser side effects when compared to intravitreal injections. The method is an excellent route for delivering hydrophilic drugs as it bypasses their rate-limiting barriers allowing more drugs to enter into the vitreous. It is an excellent route for delivering both depot forming formulations as well as for the delivery of macromolecular drugs such as Avastin (bevacizumab: a recombinant monoclonal antibody against VEGF) and insulin.

3. Retrobulbar and Peribulbar Route:

Retrobulbar injection is given through eyelid and orbital fascia and it places the drug into retrobulbar space. This mode administers the drug to the back of the eye ball and is used to

deliver drugs such as; antibiotics and corticosteroids. This route is especially applicable for the delivery of anesthetic agents as it causes minor or no change in IOP though in certain orbital diseases the reverse is also possible. Yet, it is a very delicate procedure as it may damage the optic nerve and thus requires proper expertise and equipment.

Peribulbar route for drug delivery involves injections above and/or below the globe. It is also a viable route for the delivery of anesthesia especially in cases of cataract surgery. It is a safer route compared to the retrobulbar route with reduced risk of injury. Though it is a safer method, unlike retrobulbar injection multiple cases of elevated intraocular pressure after peribulbar injections have been reported.

4. Sub-Tenon Injections:

Sub-tenon injections are administered into a cavity between tenon's capsule and sclera using a blunt cannula. Pre-operative deep sedation is also not a requirement for this procedure. Sub-tenon route appears to be a better and safer route for delivering anesthesia relative to retrobulbar and peribulbar administration since it does not require sharp needles. Steroids injected through this route have also been shown to be effective in the treatment of uveitis, cystoid macular edema, complicating uveitis and non-necrotizing scleritis.

5. Intracameral Injections:

Intracameral route is similar to intravitreal injections, but this injection delivers drug to the anterior chamber. Drugs administered through this route are limited to anterior chamber with very limited access to the posterior segment. It is generally employed for anterior segment procedures such as cataract surgery. Clinical studies have reported that intracamerally delivered dexamethasone is effective in reducing post-operative inflammation in glaucomatous and non-glaucomatous patients. It is an efficient and often a more cost-effective method of delivering antibiotics relative to topical antibiotics and antifungal agents.

5.10 FORMULATIONS FOR OCULAR DRUG DELIVERY SYSTEM

1. Conventional Delivery Systems
- (a) Eye drops
- (b) Ointments and Gels
- (c) Ocuserts and Lacriserts

2. Vesicular Systems
- (a) Liposomes
- (b) Niosomes and Discomes (Giant Niosomes)

3. Controlled Delivery Systems
- (a) Implants
- (b) Iontophoresis
- (c) Dentrimer
- (d) Microemulsion
- (e) Nanosuspension
- (f) Microneedle
- (g) Mucoadhesive Polymers

5.11 INSERTS

5.11.1 Classification of Inserts

1. Non-Erodible Inserts
   (a) Ocusert (b) Contact Lens
2. Erodible Inserts
   (a) Lacriserts (b) SODI (c) Mindisc

1. Non-Erodible Inserts:

(A) Ocuserts: It is a flat, flexible, elliptical device designed to be placed in the inferior cul-de-sac between the sclera and eyelid which releases Pilocarpine continuously at a steady state for 7 days. It comprises of 3 layers:

1. Outer Layer: Ethylene vinyl acetate copolymer layer.
2. Inner Layer: Pilocarpine gelled with alginate main polymer.
3. A retaining ring of EVA impregnated with titanium dioxide.
   Example: Pilo 20 (20 mg/hr), Pilo 40 (40 mg/hr).

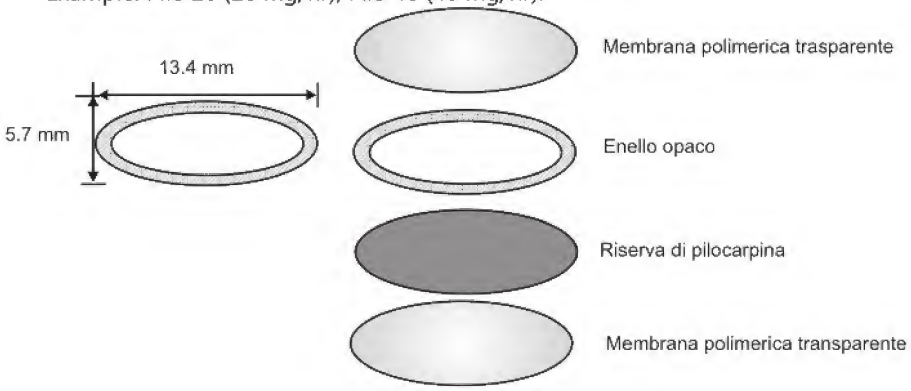


Fig. 5.7: Ocusert

Fig. 5.8: Contact Lens

(b) Contact Lens: These are circular shaped structures; dyes may be added during polymerization. Drug incorporation depends on whether the structure is Hydrophilic or Hydrophobic.

2. Erodible Inserts:

(a) Lacriserts: It is sterile rod-shaped device composed of HPC without preservative. It's weight is 5 mg, diameter is 12.5 mm and length is 3.5 mm. It is used in dry eye treatment, Keratitis Sica.

Fig. 5.9: Lacrisert

(b) SODI (Soluble Ocular Drug Insert): Inserted in Inferior Fornix.

It is a small water-soluble wafer like insert, composed of acrylamide vinyl Pyrrolidone, Ethyl acrylate. It weighs 15-16 mg. It softens in 10-15 sec., turns in viscous liquids in 10-15 minutes and after 30-60 minutes becomes polymeric solution. It is used in treatment of Glaucoma and Trachoma.

(c) Minidisc: It is made up of counter disc with convex front and concave back surface in contact with eye ball. It measures 4-5 mm in diameter. It is composed of silicon based prepolymer. For e.g. Pilocarpine, Chloramphenicol.

INTRAUTERINE DRUG DELIVERY SYSTEMS

5.12 INTRODUCTION

5.12.1 Anatomy of the Uterus

- The uterus is a pear shaped; thick walled, muscular organ suspended in the anterior wall of pelvic cavity.
- It measures normally about 3 inches long and 2 inches wide.
- Fallopian tubes enter its upper portion, one on each side and the lower portion of the uterus projects into the vagina.
- The uterine cavity is normally triangular in shape and flattened anterio-posteriorly.

The wall of the uterus consists of three layers:

1. **Endometrium:** It is the inner coat of the uterine wall and is a mucous membrane which consists of epithelium lining and connective tissue. There are two types of arteries:
   (a) Straight arteries: Supplies deeper layer.
   (b) Coiled arteries: Supplies superficial layer.

2. **Myometrium:** It is a thick, muscular middle layer made up of bundles of interlaced, smooth muscle fibers embedded in connective tissue. It is subdivided into three ill-defined, interwining muscular layers containing large blood vessels of uterine walls.
3. **Peritoneum:** It is external surface of the uterus, which is attached to both sides of the pelvic cavity by blood ligaments through which the uterine arteries cross.

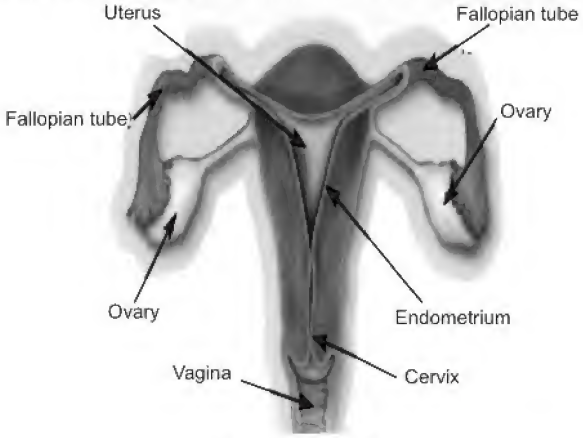


Fig. 5.10: Uterus

5.12.2 Intrauterine Devices (IUD's)

- It is the small object that is inserted through the cervix and placed in the uterus to prevent pregnancy.
- A small string hangs down from the IUD into the upper part of the vagina.
- IUD's show pharmacological efficacy for about 1-10 years. They work by changing the lining of the uterus and fallopian tubes affecting the movements of eggs and sperm and so that fertilization does not occur.

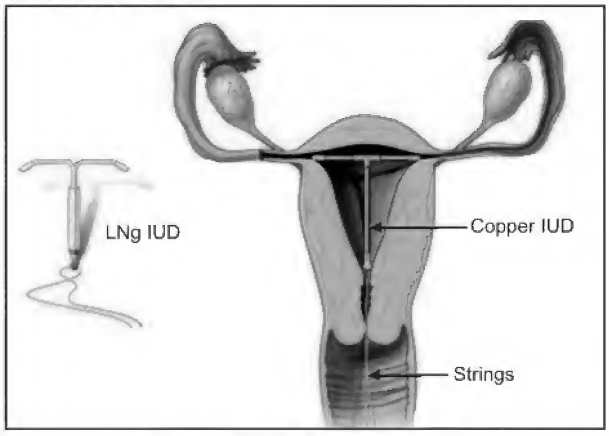


Fig. 5.11: Intrauterine Devices

5.12.3 Development of IUD's

- These devices cause more endometrial compression and myometrial distention, leading to uterine cramps, bleeding and expulsion of IUDs.
- Researchers developed IUDs in past 30 years with the aim to add antifertility agents to more tolerated, smaller devices, such as T-shaped device, to enhance effectiveness; or antifibrinolytic agents, such as e-aminocaproic acid and tranexamic acid to larger IUDs to minimize the bleeding and pain.
- Tatum developed a T-shaped device that would work better with the shape of the uterus, which forms a T when contracted. This reduced side effects significantly.
- Zipper 1968 added contraceptive metals (Cu) and Doyle and Clewe developed Progestin releasing IUD.
- This development initiated a new era of R and D for long term IU contraception, leading to generation of recent IUDs-medicated IUDs.
- Copper bearing IUDs such as Cu-7 and Progesterone releasing IUDs such as Progestasert (approved by FDA in 1976) thus evolved.

5.12.4 Types of IUDs

1. Non-medicated IUDs
2. Medicated IUDs

1. Non-medicated IUDs: These exert their contraceptive action by producing a sterile inflammatory response in the Endometrium by its mechanical interaction. These do not contain any therapeutic effect. For e.g. Ring-Shaped IUDs of Stainless Steel, Plastic IUDs, Lippes Loop, Dalkon Shield, Saf-T-Coil.

2. Medicated IUDs: These are capable of delivering pharmacologically active antifertility agents. For e.g. Copper bearing IUDs, Progesterone releasing IUD.

There are two types of medicated IUDs:

1. Copper bearing IUDs.
2. Hormone releasing IUDs: There are two types:
   (a) Progesterone releasing IUD - Progestasert.
   (b) Levonorgesterone IUD - Levonorgestrel releasing device - [MIRENA].

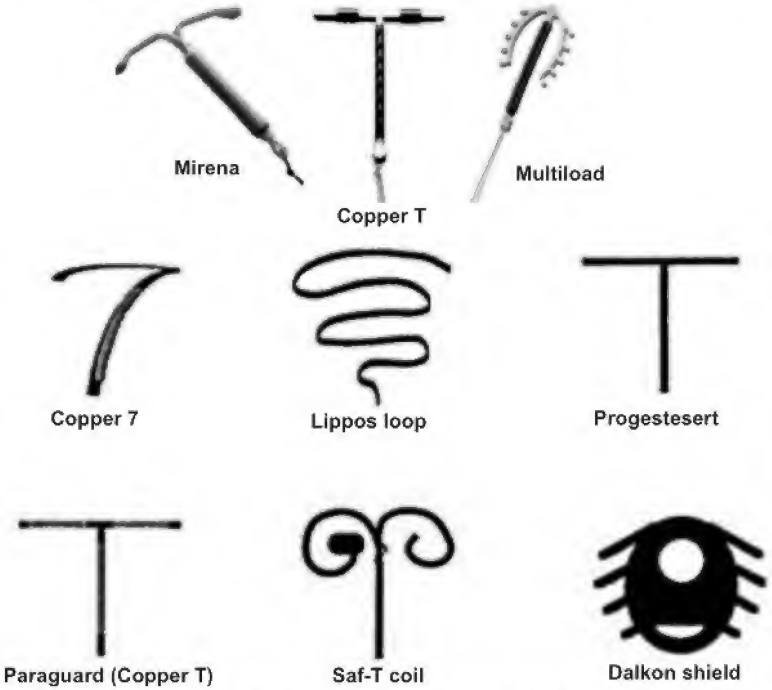


Fig. 5.12: Types of Intrauterine Devices

5.12.5 Advantages of IUD's

The IUD is one of the most popular contraceptive methods, especially for long-term reversible contraception, as it can be easily fitted and removed.

- It is highly effective, with a 98-99% success rate over five years of IUD use.
- It can be used by almost any woman including nulliparous.
- Its action lasts for ten years if it is not removed inbetween.
- The onset of action is immediate.
- It is suitable for lactating women.
- Fertility returns promptly on discontinuation.
- It can be used by women who are on any type of medication.
- It is not associated with cancer of any organ unlike hormonal contraception.
- It is cost effective.

5.12.6 Disadvantages of IUD's

- Menorrhagia is a frequent complaint, as are dysmenorrhoea and polymenorrhoea. These are the major reasons for IUD discontinuation.
- It does not offer any protection against sexually transmitted infections (STIs).

- There is a slight risk (1%) of acquiring uterine infection during IUD insertion within 20 days of the procedure. This is increased if the woman is prone to STIs. Women should be tested for gonorrhea or chlamydia before insertion, and for any other organism if they so request. Fortunately, pelvic infections with the IUD in utero can be treated adequately without removing the device.
- Expulsion of the IUD may occur especially following or during the periods in the first three months.
- Uterine perforation may occur in 0.1% of women during insertion. This may manifest as lower abdominal pain. Perforation will require surgical removal.
- There is a higher risk of ectopic pregnancy if conception occurs with an IUD in situ, though pregnancies are very rare with this method.
- Nausea, Vomiting, Headache and Weight gain are some of the side effects.

5.12.7 Applications of IUD's

- It is used as a contraceptive to prevent pregnancy.
- It can be suitable for use in Hormone Replacement Therapy.
- It can be safely used in women with heavy bleeding to prevent/control the same.
- In the treatment of fibroids.

QUESTIONS

1. Explain the Ocular Drug Delivery System and add a note on types of approaches used in it.
2. Enlist and explain the barriers to Ocular Drug Delivery System.
3. Enlist and explain the methods to overcome barriers to Ocular Drug Delivery System.
4. Write a note on the various formulations for Ocular Drug Delivery System.
5. Define and classify Inserts. Explain with suitable examples.
6. Write a note on IUD's.
7. Define and classify the various IUD's.
8. Give the advantages and disadvantages of IUD's.
9. Differentiate the Medicated and Non-Medicated IUD's.
10. What are Progestasert?
11. What is MIRENA?

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INDEX